

IN THE CLAIMS

Please cancel claims ~~1-37, 41, 43-54, 58-60, 61, 63-65, 67, 69-78, 84-87, 94,~~
97, 101, 103, 105-111, 113, 115-117, 132, 136, 137, and 140-153.

Please cancel claims 38, 39, 40, 42, 55, 88, 118, and 138 and substitute
therefore amended claims 38, 39, 40, 42, 55, 88, 118, and 138 set forth in Appendix 3.

REMARKSIn The Specification

The specification amendments are set forth in Appendices 1-2. Appendix 1 sets forth the amended specification paragraphs. Appendix 2 shows the amended paragraphs with additions indicated by underlining and deletions indicated by bracketing.

Applicants' amendments to the specification add a reference to related applications and correct typographical errors. None of these amendments add new matter.

In The Claims

The claim amendments are set forth in Appendices 3-4. Appendix 3 sets forth the amended claims. Appendix 4 shows the amended claims with additions indicated by underlining and deletions indicated by bracketing. These amendments are summarized below.

Applicants have canceled claims 1-37, 41, 58-60, 61, 63-65, 67, 69-78, 84-87, 94, 97, 101, 103, 105-111, 113, 115-117, 132, and 140-153 and have amended claims 88 and 118 to refer to fewer claims, thereby reducing this application's filing fee. Applicants have amended claim 40 to delete a compound that they are no longer claiming in this application and to recite the subject matter of claim 41 (now cancelled). Applicants have amended claim

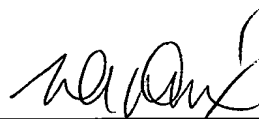
42 to delete its recitation of an intended use and have therefore cancelled claims 43-54, 136, and 137 for reciting specific uses. Applicants have amended claims 38, 39, 40, 42, 55, and 138 to refer to pending claims.

These amendments are made without prejudice and without waiver of applicants' right to pursue the non-elected subject matter in applications claiming priority herefrom.

None of these amendments adds new matter.

Applicants request consideration of the application and early allowance of the pending claims.

Respectfully submitted,



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APPENDIX 1Amended Specification Paragraphs

Please add as a first paragraph, immediately after the title:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of co-pending United States patent application 09/773,477, filed January 31, 2001, which is a divisional of co-pending United States patent application 09/400,639, filed September 21, 1999, now patent no. 6,258,948, which is a divisional of co-pending United States patent application 08/761,483, now patent no.

A' 6,204,261, filed December 6, 1996, which is a continuation-in-part of co-pending United States provisional patent application 60/031,495, filed November 26, 1996, which is a continuation-in-part of co-pending United States patent application 08/712,878, now patent no. 5,985,863, filed September 12, 1996, and also a continuation-in-part of co-pending United States patent application 08/598,332, filed February 8, 1996, now patent no. 5,874,424, which is a continuation-in-part of co-pending United States patent application 08/575,641, filed December 20, 1995, now patent no. 6,008,217.

Please delete the paragraph that begins at page 17, line 15 and substitute therefore:

A² The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen. Heterocycles defined above include, for example, pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, purinyl, pyrimidyl, indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β -carbolinyl, tetrazolyl, thiazolidinyl, benzofuranyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrrolidinyl, oxazepinyl, azepinyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl and sulfolanyl. Further heterocycles are described in A.R. Katritzky and C.W. Rees, eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds, Vol. 1-8, Pergamon Press, NY (1984).

Please delete the paragraph that begins at page 300, line 15 and substitute therefore:

A3 The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as those described in Pharmacopeia Helvetica or a similar alcohol.

Please delete the paragraph that begins at page 322,
line 2 and substitute therefore:

Aliquots of plasma (150 μ l) were treated with 5% perchloric acid (5 μ l) then mixed by vortexing and allowed to stand for 90 minutes prior to centrifugation. The resulting supernatant was separated and 20 μ l was injected for HPLC analysis.

A4
HPLC Conditions

Column	100 x 4.6mm	Kromasil KR 100 5C4
Mobile Phase	0.1m Tris pH7.5	86%
	Acetonitrile	14%
Flowrate	1ml/min	
Detection	UV at 210nm	
Retention Time	3.4 mins	

Please delete the paragraph that begins at page 324,
line 12 and ends at line 19 and substitute therefore:

A5
The whole blood assay is a simple method for measuring the production of IL-1 β (or other cytokines) and the activity of potential inhibitors. The complexity of this assay system, with its full complement of lymphoid and inflammatory cell types, spectrum of plasma proteins and red blood cells is an ideal in vitro representation of human in vivo physiologic conditions.

Please delete the paragraph that begins at page 331,
line 12 and ends at line 18 and substitute therefore:

The efficacy of analogs of **214e** were also evaluated
in LPS challenged mice after IP administration (**Fig. 9**) and PO
administration
(**Fig. 10**).

A6

Table 3 % Inhibition of IL- β production by analogs of **214e** in
LPS-challenged mice after PO and IP administration (50 mg/kg).

Please delete the paragraph that begins at page 345,
line 20 and ends at line 22 and substitute therefore:

Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-
benzyloxyprolinyl))-3-amino-4-oxobutanoic acid
tert-butyl ester semicarbazone.

A7

Please delete the paragraph that begins at page 345,
line 28 and substitute therefore:

¹H NMR (500MHz, CD₃OD) δ 7.35-7.2 (m, 6H), 7.0 (d,
2H), 6.65 (d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H), 4.3 (br. m,
1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m, 1H), 2.75-2.6 (m,
3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95
(d, 3H), 0.90 (s, 3H).

A8

Please delete the paragraph that begins at page 346,
line 3 and substitute therefore:

A9 Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid.

Please delete the paragraph that begins at page 362, line 22 and substitute therefore:

(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R).

A10 A solution of the ester 68a (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N₂. The solution was then reduced *in vacuo*, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form (c 50%), and its acyloxy keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C; $[\alpha]_D^{24}$ -33.2°* (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; ¹H NMR (CD₃OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscured m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for

★

A10

$C_{31}H_{37}N_5O_{10} \cdot 3H_2O$: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 ($M^+ + 1$); 435, 147.

Please delete the paragraph that begins at page 363, line 16 and substitute therefore:

A11

(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; S), was prepared according to the method described for the acid 69a which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD_3OD , consisting of the keto form, and its acyloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); $[\alpha]_D^{24}$ -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; 1H NMR (d_6 -DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, $J = 6.2$), 8.10 (2H, m), 7.83 (1H, d, $J = 8.7$), 7.61 (1H, t, $J = 8.2$), 7.46 (1H, d, $J = 8.2$), 7.08 (3H, m), 6.65 (2H, d, $J = 8.3$), 5.50 (1H, q, $J = 6.5$), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79 (3H, s), 1.23 (3H, d, $J = 7.0$), 0.82 (6H, m). Anal. Calcd. for $C_{31}H_{37}N_5O_{10} \cdot 1.5H_2O$: C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 ($M^+ + 1$, 22%); 107 (100).

Please delete the paragraph that begins at page 375,
line 28 and substitute therefore:

A12
(3S) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a). t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C; $[\alpha]_D^{22}$ -27.7 ° (c 0.2, CH₂Cl₂); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ¹H NMR (CDCl₃) δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

Please delete the paragraph that begins at page 384,
line 25 and substitute therefore:

(1S,9S) t-Butyl 9-acetyl-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a]-[1,2]diazepine-1-carboxylate

A13 (211c). Acetic anhydride (307mg, 3.01mmol) was added to a

stirred mixture of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 813.7mg, 2.74mmol), diisopropylethylamine (884mg, 6.84mmol) and CH₂Cl₂ (20ml). The mixture was kept for 1h then diluted with EtOAc, washed with NaHCO₃ solution then brine, dried (MgSO₄) and concentrated to yield a colourless oil. The product was purified by flash chromatography (0.5-8% MeOH/CH₂Cl₂) to afford **211c** (804mg, 71%) of colourless powder: mp 162-3 °C; $[\alpha]_D^{23}$ -109 (c 1.03, CH₂Cl₂); IR(KBr) 3358, 2974, 1733, 1693, 1668, 1528, 1462, 1431, 1406, 1371, 1278, 1271, 1250, 1233, 1217, 1154, 1124; ¹H NMR (CDCl₃) δ 6.32 (1H, d), 5.29-5.25 (1H, m), 4.98-4.85 (1H, m), 4.68-4.58 (1H, m), 3.55-3.39 (1H, m), 2.91-2.66 (2H, m), 2.39-2.18 (2H, m), 2.03 (3H, s), 1.88-1.64 (4H, m), 1.47 (9H, s); Anal. Calcd for C₁₆H₂₅N₃O₅: C, 56.62; H, 7.43; N, 12.38. Found: C, 56.62; H, 7.43; N, 12.36; MS (+ FAB) 340 (M⁺ + 1, 40%), 284 (100%).

Please delete the paragraph that begins at page 435, line 4 and substitute therefore:

[3S (2S)] t-Butyl 1-benzyloxycarbonyl-2-(3-benzyloxycarbonylamino-2-phthalimidopropionyl)pyridazine-3-carboxylate (267). A suspension of the acid **266** (1.32g, 3.58mmol) in dry ether (37ml) was treated with phosphorus pentachloride (1.04g, 5mmol) and stirred at room temperature for 2h. The solution was filtered to remove unreacted

A14 phosphorus pentachloride then evaporated to dryness. The residue was treated with dry toluene (25ml) then evaporated to dryness. This process was repeated several times. The resulting oil was dissolved in dry dichloromethane (25ml), cooled to 0 °C and treated with a solution of (3S) t-butyl 1-benzyloxycarbonylpyridazine-3-carboxylate (1.15g, 3.58mmol) in dry dichloromethane (2ml) followed by 5% aqueous sodium bicarbonate solution (25ml). The mixture was stirred rapidly at room temperature for 20h then diluted with ethyl acetate (100ml) and acidified to pH2 with 1M HCl. The organic phase was washed twice with dilute HCl solution then brine, dried (MgSO₄) and concentrated. The resulting oil was purified by flash chromatography (2-20% ethyl acetate/dichloromethane then 10-20% methanol/dichloromethane) to afford (267), 1.25g (52%) as a white powder: IR (KBr) 3367, 2955, 1722, 1517, 1455, 1387, 1369, 1251, 1153, 721; ¹H NMR (CDCl₃) δ 7.81 (2H, m), 7.74 (2H, m), 7.63 (1H, brs), 7.31 (10H, m), 5.46-4.76 (5H, m), 4.07-3.54 (4H, m), 2.4 (1H, m), 2.0-1.6 (3H, m), 1.40 (9H, s); MS (ES+), 671 (M + 1), 693 (M + Na).

Please delete the paragraph that begins at page 481, line 7 and substitute therefore:

A15 (3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).

Step A. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-

dimethylphenylamino)-propionic acid. Prepared by a method similar as described for 600a/103 (Step A), except 2-fluoro-4,6-dimethyl-nitrobenzene was used instead of 2-fluoronitrobenzene to give the desired compound in 93% yield.

A15

Please delete the paragraph that begins at page 481, line 16 and substitute therefore:

Step B. (2S)-2-tert-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenyl-amino)propionic acid was converted to the title compound in quantitative yield as described in the preparation of 600a/103 (Step B).

A16

Please delete the paragraph that begins at page 494, line 24 and substitute therefore:

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605m). 64.5 mg (34%) as a white solid: ¹H NMR (DMSO-d₆, existing as diastereomers of the hemiacetal & open form of the aldehyde) δ 9.48 (0.2H, s), 8.85-8.72 (1H, m), 8.65-8.60 (0.8 H, d), 8.30-8.26 (0.2 H, d), 7.95-7.88 (2H,d), 7.6-7.45 (6H, m), 7.44-7.38 (1H, m), 5.78-5.75 (0.2H, d), 5.48 (0.6H, s), 4.85-4.70 (2H, m), 4.62-4.54 (1H, d), 4.50-4.40 (2H, m), 4.25-4.14 (1H, m), 3.9-3.85 (1H, m), 3.16 (3H, s), 3.05-2.3 (2, m).

A17

Please delete the paragraph that begins at page 495,
line 6 and substitute therefore:

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(naphthylene-2-carbonyl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-
A18 butyric acid (605n). 103 mg (17%) as a white solid: ^1H NMR
(CD_3OD) δ 1.9(s, 3H), 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H),
4.3(m, 1H), 4.5-4.7(m, 3H), 4.85-5.1(m, 2H), 7.3-7.65(m, 6H),
7.85-8.05(m, 4H), 8.45(s, 1H).

Please delete the paragraph that begins at page 498,
line 5 and substitute therefore:

A19 Step A. A solution of **204** (223 mg, 0.5 mmol) and **603r** (300mg;
0.36 mmol) in 4 ml of DMF and 4 ml of CH_2Cl_2 was treated with
(Ph_3P) $_2\text{PdCl}_2$ (10 mg), 1-hydroxybenzotriazole (135 mg, 1.0 mmol)
and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride (115 mg, 0.6 mmol). Tri-n-butyl tin hydride
(219 mg, 0.75 mmol) was added dropwise to the reaction and
stirred for 18 h. The reaction was poured onto EtOAc and
washed with aq. 10% NaHSO_4 , sat. aq. NaHCO_3 and sat. aq. NaCl ,
dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography
(flash, SiO_2 , 0% to 50% EtOAc/hexane) gave 360 mg (86%) of
607a as a foam.

Please delete the paragraph that begins at page 528,
line 8 and substitute therefore:

A20 [1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-isopropoxy-5-oxo-tetrahydro-furan-3-yl)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamide (2100a). A solution of 214e (101 mg, 0.23 mmol) in isopropanol (10 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (10 mg). After 75 minutes, the reaction mixture was poured into saturated NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography (SiO₂, CH₂Cl₂ to EtOAc) afforded 56 mg (51%) of 2100a as a white solid: ¹H NMR (CDCl₃; mixture of diastereomers) δ 7.9-7.8 (2H,m), 7.6-7.5 (1H, m), 7.5-7.4 (2H, m), 7.1 (0.5H, d), 6.9 (0.5H, d), 6.4 (0.5H,d), 5.6 (0.5H, d), 5.3 (0.5H, s), 5.2-5.1 (1H, m), 4.95 (0.5H, m), 4.75-4.5 (1.5H, m), 4.35 (0.5H, t), 4.1 (0.5H, m), 3.98 (0.5H, m), 3.3-2.75 (4H, m), 2.5-2.4 (2H,m), 2.25 (1H, m), 2.1-1.9 (3H,m) 1.75-1.55 (2H,m).

Please delete the paragraph that begins at page 529, line 10 and substitute therefore:

A21 [3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diethoxy-butyric acid, ethyl ester (2100b). A solution of 214e (16 mg, 0.036 mmol) in ethanol (2 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (2 mg). After 5

days, the reaction mixture was poured into saturated NaHCO_3 and extracted with CH_2Cl_2 . The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2 , CH_2Cl_2 :EtOAc 95:5 v/v) afforded 16 mg (81%) of **2100b** as a

A2' white solid: ^1H NMR (CDCl_3) δ 7.85-7.74 (2H,m), 7.55-7.38 (3H,m), 7.04-6.95 (1H,d), 6.61-6.48 (1H,d), 5.15-5.08 (1H,m), 4.63-4.53 (1H,m), 4.52-4.45 (1H,m), 4.42-4.35 (1H,m), 4.15-4.05 (2H,m), 3.74-3.60 (2H,m), 3.57-3.42 (2H,m), 3.39-3.28 (1H,m), 3.03-2.93 (1H,m), 2.92-2.82 (1H,m), 2.65-2.52 (2H,m), 2.42-2.25 (1H,m), 2.20-1.88 (4H,m), 1.76-1.50 (2H,m), 1.35-1.10 (9H,m).

APPENDIX 2Amended Specification Paragraphs Marked to Show Amendments

The following was added as a first paragraph, immediately after the title:

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The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen. Heterocycles defined above include, for example, pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, purinyl, pyrimidyl, indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β -carbolinyl, tetrazolyl, thiazolidinyl, [benzofuranoyl] benzofuranyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, [oxopyrrolidinyl, oxoazepinyl] oxopyrrolidinyl, oxazepinyl, azepinyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl and sulfolanyl. Further heterocycles are described in A.R. Katritzky and C.W. Rees, eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis

and Use of Heterocyclic Compounds,* Vol. 1-8, Pergamon Press, NY (1984).

The paragraph that begins at page 300, line 15 was amended as follows:

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol

* Text underlined in the original.

diluent or dispersant such as [Ph. Helv]* those described in Pharmacopeia Helvetica or a similar alcohol.

The paragraph that begins at page 322, line 2 was amended as follows:

Aliquots of plasma (150µl) were treated with 5% perchloric acid (5µl) then mixed by vortexing and allowed to stand for 90 minutes prior to centrifugation. The resulting supernatant was separated and 20µl was injected for HPLC analysis.

HPLC Conditions**

Column	100 x 4.6mm	Kromasil KR 100 5C4
Mobile Phase	0.1m Tris [ph7.5] <u>pH7.5</u>	86%
	Acetonitrile	14%
Flowrate	1ml/min	
Detection	UV at 210nm	
Retention Time	3.4 mins	

The paragraph that begins at page 324, line 12 and ends at line 19 was amended as follows:

The whole blood assay is a simple method for measuring the production of [IL-1b] IL-1β (or other cytokines) and the activity of potential inhibitors. The complexity of

* Text underlined in the original.

** Text underlined in the original.

this assay system, with its full complement of lymphoid and inflammatory cell types, spectrum of plasma proteins and red blood cells is an ideal in vitro* representation of human in vivo** physiologic conditions.

The paragraph that begins at page 331, line 12 and ends at line 18 was amended as follows:

The efficacy of analogs of **214e** were also evaluated in LPS challenged mice after IP administration (**Fig. 9**) and PO administration (**Fig. 10**).

Table 3*** % Inhibition of IL- β production by analogs of **214e** in [LPS-challenged] LPS-challenged mice after PO and IP administration (50 mg/kg).

The paragraph that begins at page 345, line 20 and ends at line 22 was amended as follows:

Step B. [N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid tert-butyl ester semicarbazone.]****

* Text underlined in the original.

** Text underlined in the original.

*** Text underlined in the original.

**** Text underlined in the original.

N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid
tert-butyl ester semicarbazone.*

The paragraph that begins at page 345, line 28 was amended as follows:

¹H NMR (500MHz, CD₃OD) δ 7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65(d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H), 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m, [IH] 1H), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

The paragraph that begins at page 346, line 3 was amended as follows:

Step C. [N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.]**
N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid.***

* Text underlined in original. Changes highlighted in bold.

** Text underlined in the original.

*** Text underlined in original. Changes highlighted in bold.

The paragraph that begins at page 362, line 22 was amended as follows:

(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R).*

A solution of the ester 68a (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N₂. The solution was then reduced *in vacuo*, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form (c 50%), and its [acycloxy] acyloxy keto form (two isomers at C-4, c 50%): m.p.

decomposes above 150°C; $[\alpha]_D^{24}$ -33.2° (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; ¹H NMR (CD₃OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, [obscurred] obscured m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for C₃₁H₃₇N₅O₁₀ · 3H₂O: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 (M⁺ + 1); 435, 147.

* Text underlined in the original.

The paragraph that begins at page 363, line 16 was amended as follows:

(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; S),* was prepared according to the method described for the acid 69a which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form, and its [acycloxy] acyloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); $[\alpha]_D^{24}$ -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; ¹H NMR (d₆-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, J = 6.2), 8.10 (2H, m), 7.83 (1H, d, J = 8.7), 7.61 (1H, t, J = 8.2), 7.46 (1H, d, J = 8.2), 7.08 (3H, m), 6.65 (2H, d, J = 8.3), 5.50 (1H, q, J = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79 (3H, s), 1.23 (3H, d, J = 7.0), 0.82 (6H, m). Anal. Calcd. for C₃₁H₃₇N₅O₁₀ · 1.5H₂O: C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 (M⁺ + 1, 22%); 107 (100).

* Text underlined in the original.

The paragraph that begins at page 375, line 28 was amended as follows:

(3S) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a). t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C; $[\alpha]_D^{22}$ -27.7 ° (c 0.2, CH₂Cl₂); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ¹H NMR (CDCl₃) [d] δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

The paragraph that begins at page 384, line 25 was amended as follows:

(1S,9S) t-Butyl 9-acetyl-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a]-[1,2]diazepine-1-carboxylate (211c). Acetic anhydride (307mg, 3.01mmol) was added to a

stirred mixture of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 813.7mg, 2.74mmol), diisopropylethylamine (884mg, 6.84mmol) and CH_2Cl_2 (20ml). The mixture was kept for 1h then diluted with EtOAc, washed with NaHCO_3 solution then brine, dried (MgSO_4) and concentrated to yield a colourless oil. The product was purified by flash chromatography (0.5-8% MeOH/ CH_2Cl_2) to afford **211c** (804mg, 71%) of colourless powder: mp 162-3 °C; $[\alpha]_{\text{D}}^{23}$ -109 ° 1.03, CH_2Cl_2); IR(KBr) 3358, 2974, 1733, 1693, 1668, 1528, 1462, 1431, 1406, 1371, 1278, 1271, 1250, 1233, 1217, 1154, 1124; $[\delta]$ ^1H NMR (CDCl_3) [d] δ 6.32 (1H, d), 5.29-5.25 (1H, m), 4.98-4.85 (1H, m), 4.68-4.58 (1H, m), 3.55-3.39 (1H, m), 2.91-2.66 (2H, m), 2.39-2.18 (2H, m), 2.03 (3H, s), 1.88-1.64 (4H, m), 1.47 (9H, s); Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_5$: C, 56.62; H, 7.43; N, 12.38. Found: C, 56.62; H, 7.43; N, 12.36; MS (+ FAB) 340 ($\text{M}^+ + 1$, 40%), 284 (100).

The paragraph that begins at page 435, line 4 was amended as follows:

[3S (2S)] t-Butyl 1-benzyloxycarbonyl-2-(3-benzyloxycarbonylamino-2-phthalimidopropionyl)pyridazine-3-carboxylate (267). A suspension of the acid **266** (1.32g, 3.58mmol) in dry ether (37ml) was treated with phosphorus pentachloride (1.04g, 5mmol) and stirred at room temperature for 2h. The solution was filtered to remove unreacted

phosphorus pentachloride then evaporated to dryness. The residue was treated with dry toluene (25ml) then evaporated to dryness. This process was repeated several times. The resulting oil was dissolved in dry dichloromethane (25ml), cooled to 0 °C and treated with a solution of (3S) t-butyl 1-benzyloxycarbonylpyridazine-3-carboxylate (1.15g, 3.58mmol) in dry dichloromethane (2ml) followed by 5% aqueous sodium bicarbonate solution (25ml). The mixture was stirred rapidly at room temperature for 20h then diluted with ethyl acetate (100ml) and acidified to pH2 with 1M HCl. The organic phase was washed twice with dilute HCl solution then brine, dried (MgSO₄) and concentrated. The resulting oil was purified by flash chromatography (2-20% ethyl acetate/dichloromethane then 10-20% methanol/dichloromethane) to afford (267), 1.25g (52%) as a white powder: IR (KBr) 3367, 2955, 1722, 1517, 1455, 1387, 1369, 1251, 1153, 721; [¹H NMR] ¹H NMR (CDCl₃) δ 7.81 (2H, m), 7.74 (2H, m), 7.63 (1H, brs), 7.31 (10H, m), 5.46-4.76 (5H, m), 4.07-3.54 (4H, m), 2.4 (1H, m), 2.0-1.6 (3H, m), 1.40 (9H, s); MS (ES+), 671 (M + 1), 693 (M + Na).

The paragraph that begins at page 481, line 7 was amended as follows:

[(3S)-2-Oxo3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).]

(3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).

Step A.* (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenylamino)-propionic acid. Prepared by a method similar as described for 600a/103 (Step A), except 2-fluoro-4,6-dimethyl-nitrobenzene was used instead of 2-fluoronitrobenzene to give the desired compound in 93% yield.

The paragraph that begins at page 481, line 16 was amended as follows:

Step B.** (2S)-2-tert-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenyl-amino)propionic acid was converted to the title compound in [quantitative] quantitative yield as described in the [prepartation] preparation of 600a/103 (Step B).

The paragraph that begins at page 494, line 24 was amended as follows:

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605m). 64.5 mg (34%) as a white solid: ¹H NMR (DMSO-

* Text underlined in the original.

** Text underlined in the original.

d_6 , [exisitng] existing as diastereomers of the hemiacetal & open form of the aldehyde) δ 9.48 (0.2H, s), 8.85-8.72 (1H, m), 8.65-8.60 (0.8 H, d), 8.30-8.26 (0.2 H, d), 7.95-7.88 (2H,d), 7.6-7.45 (6H, m), 7.44-7.38 (1H, m), 5.78-5.75 (0.2H, d), 5.48 (0.6H, s), 4.85-4.70 (2H, m), 4.62-4.54 (1H, d), 4.50-4.40 (2H, m), 4.25-4.14 (1H, m), 3.9-3.85 (1H, m), 3.16 (3H, s), 3.05-2.3 (2, m).

The paragraph that begins at page 495, line 6 was amended as follows:

[(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(naphthylene-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605n).] [(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(naphthylene-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605n). 103 mg (17%) as a white solid: ^1H NMR (CD_3OD) δ 1.9(s, 3H), 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 4.3(m, 1H), 4.5-4.7(m, 3H), 4.85-5.1(m, 2H), 7.3-7.65(m, 6H), 7.85-8.05(m, 4H), 8.45(s, 1H).

The paragraph that begins at page 498, line 5 was amended as follows:

Step A.* A solution of **204** (223 mg, 0.5 mmol) and **603r** (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH_2Cl_2 was treated with

* Text underlined in the original.

(Ph₃P)₂PdCl₂ (10 mg), [1-hydroxybenzotriazole]
1-hydroxybenzotriazole (135 mg, 1.0 mmol) and 1-(3-
 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115
 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol)
 was added dropwise to the reaction and stirred for 18 h. The
 reaction was poured onto EtOAc and washed with aq. 10% NaHSO₄,
 sat. aq. NaHCO₃ and sat. aq. NaCl, dried over Na₂SO₄ and
 concentrated *in vacuo*. Chromatography (flash, SiO₂, 0% to 50%
 EtOAc/hexane) gave 360 mg (86%) of **607a** as a foam.

The paragraph that begins at page 528, line 8 was
 amended as follows:

**[1*S*, 9*S* (2*RS*, 3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-
 octahydro-N-(2-isopropoxy-5-oxo-tetrahydro-furan-3-yl)-6H-
 pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamide (2100a).** A
 solution of **214e** (101 mg, 0.23 mmol) in isopropanol (10 ml)
 was stirred at room temperature with a catalytic amount of *p*-
 toluenesulfonic acid (10 mg). After 75 minutes, the reaction
 mixture was poured into saturated NaHCO₃ and extracted with
 CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and
 concentrated. Flash chromatography (SiO₂, CH₂Cl₂ to EtOAc)
 afforded 56 mg (51%) of **2100a** as a white solid: ¹H NMR
 (CDCl₃; mixture of diastereomers) δ 7.9-7.8 (2H, m), 7.6-7.5
 (1H, m), 7.5-7.4 (2H, m), 7.1 (0.5H, d), 6.9 (0.5H, d), 6.4
 (0.5H, d), 5.6 (0.5H, d), 5.3 [(0.5H, s)] (0.5H, s), 5.2-5.1
 (1H, m), 4.95 (0.5H, m), 4.75-4.5 (1.5H, m), 4.35 (0.5H, t),

4.1 (0.5H, m), 3.98 (0.5H, m), 3.3-2.75 (4H, m), 2.5-2.4 (2H,m), 2.25 (1H, m), 2.1-1.9 (3H,m) 1.75-1.55 (2H,m).

The paragraph that begins at page 529, line 10 was amended as follows:

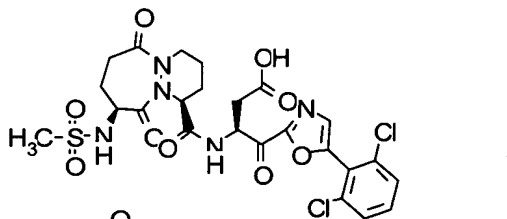
[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxamido)-4,4-diethoxy-butyric acid, ethyl ester (2100b). A solution of **214e** (16 mg, 0.036 mmol) in ethanol (2 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (2 mg). After 5 days, the reaction mixture was poured into saturated NaHCO₃ and extracted with CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography (SiO₂, CH₂Cl₂:EtOAc 95:5 v/v) afforded 16 mg (81%) of **2100b** as a white solid: ¹H NMR (CDCl₃) [d] δ 7.85-7.74 (2H,m), 7.55-7.38 (3H,m), 7.04-6.95 (1H,d), 6.61-6.48 (1H,d), 5.15-5.08 (1H,m), 4.63-4.53 (1H,m), 4.52-4.45 (1H,m), 4.42-4.35 (1H,m), 4.15-4.05 (2H,m), 3.74-3.60 (2H,m), 3.57-3.42 (2H,m), 3.39-3.28 (1H,m), 3.03-2.93 (1H,m), 2.92-2.82 (1H,m), 2.65-2.52 (2H,m), 2.42-2.25 (1H,m), 2.20-1.88 (4H,m), 1.76-1.50 (2H,m), 1.35-1.10 (9H,m).

APPENDIX 3

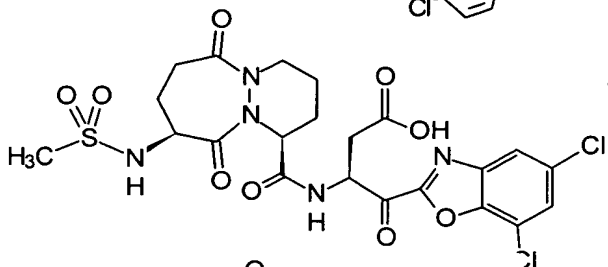
Amended Claims

38. The compound according to claims 62 or 68,
selected from the group consisting of:

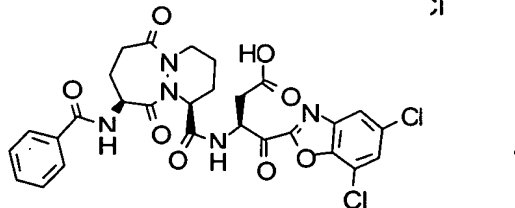
220b



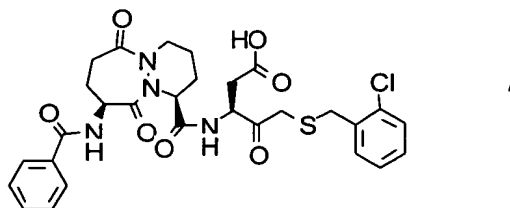
223b



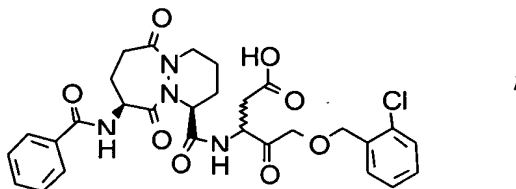
223e



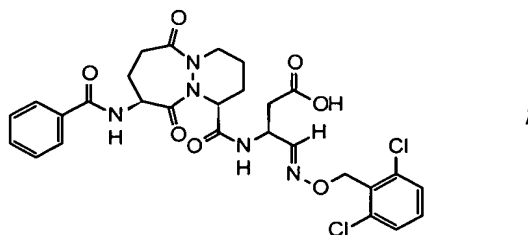
226e



227e

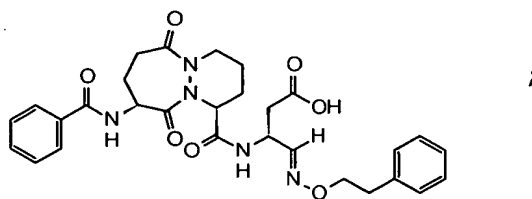


307a

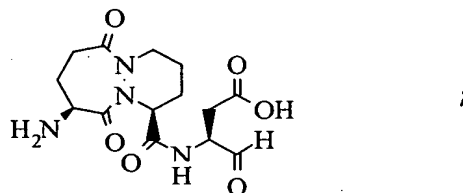


A22

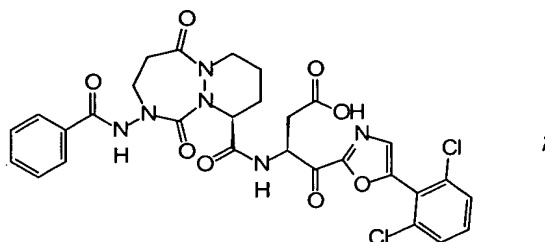
307b



429

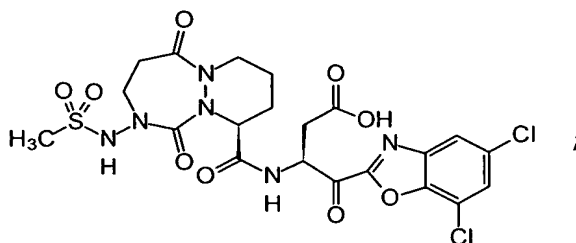


820b

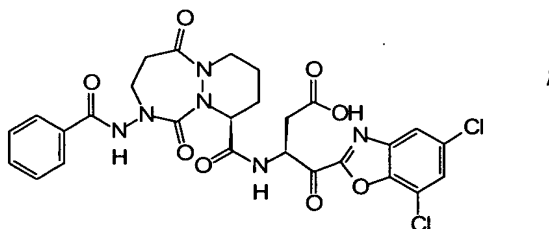


A22

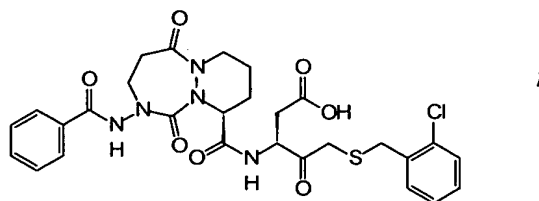
823b



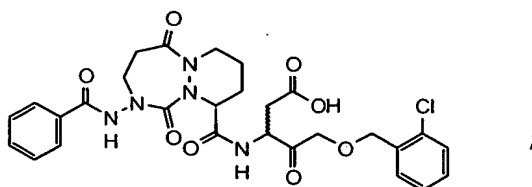
823e



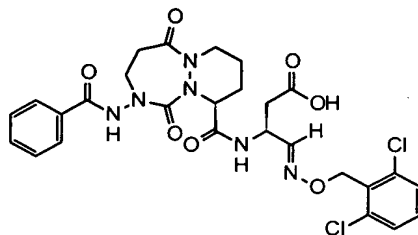
826e



827e

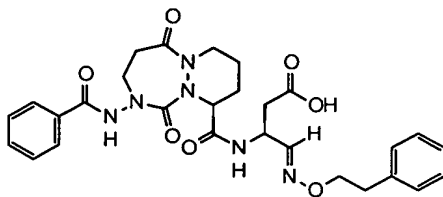


907a



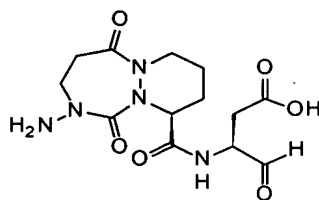
;

907b



; and

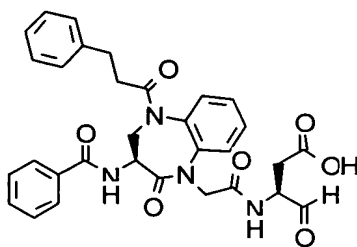
1029



A22

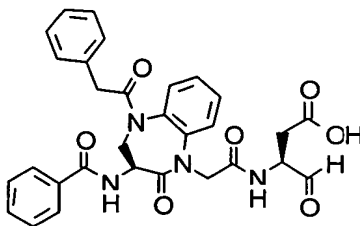
39. The compound according to claim 62; selected from the group consisting of:

605a



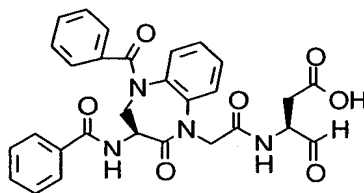
;

605b

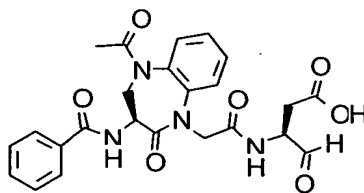


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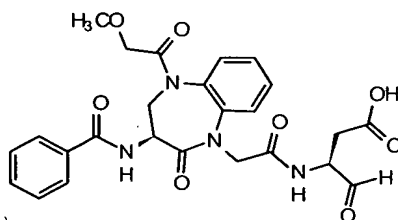
605c



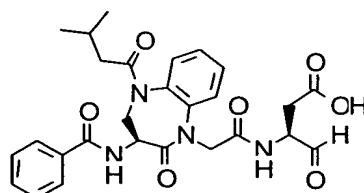
605d



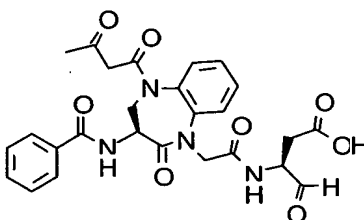
605e



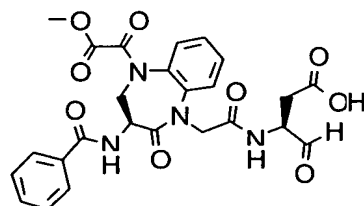
605f



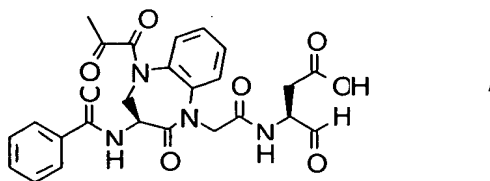
605g



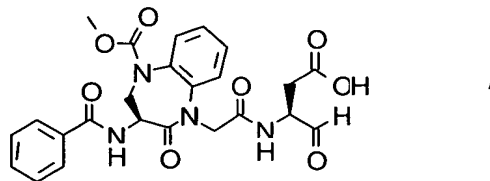
605h



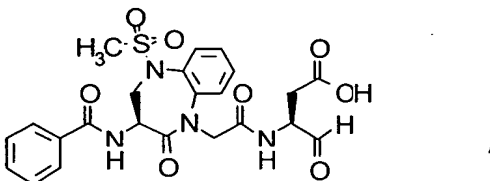
605i



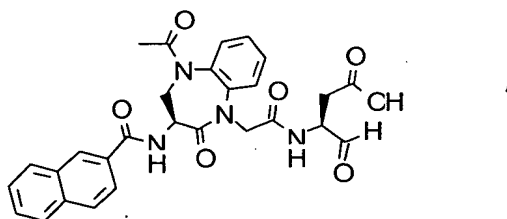
605j



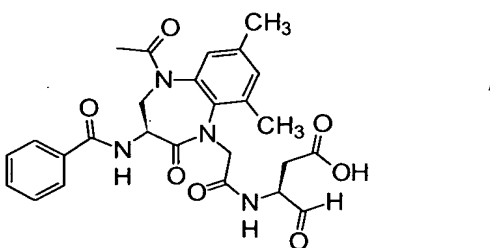
605m



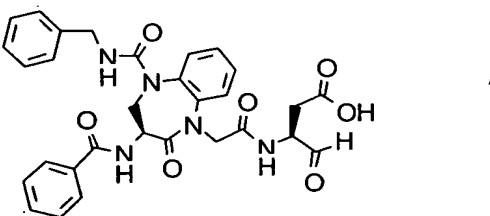
605n



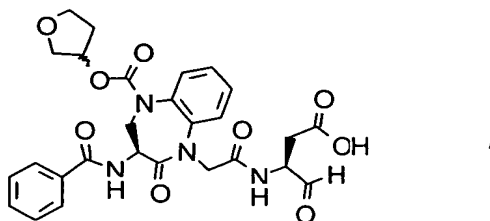
6050



605p

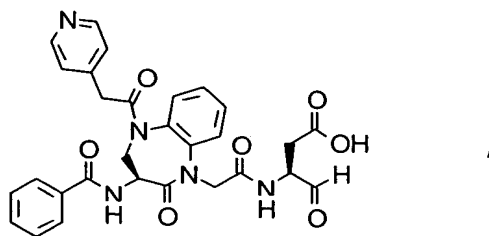


605q

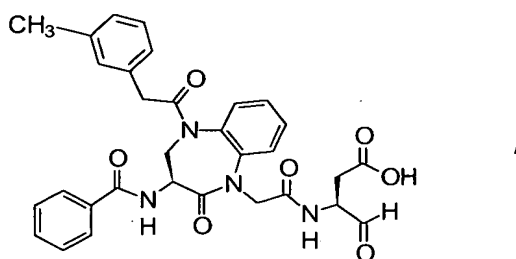


A22

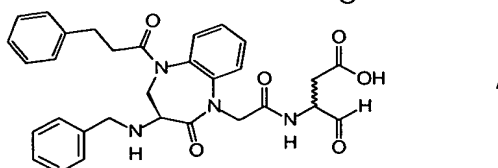
605s



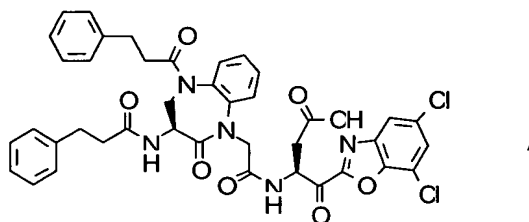
605t



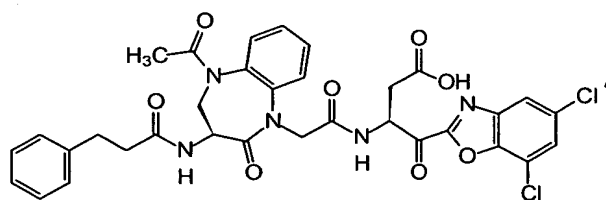
605v



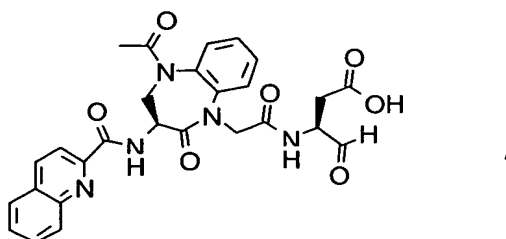
609a



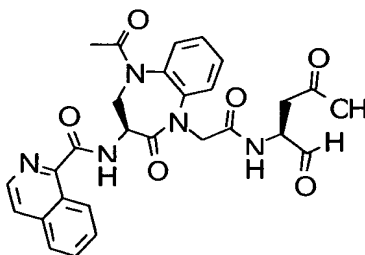
609b



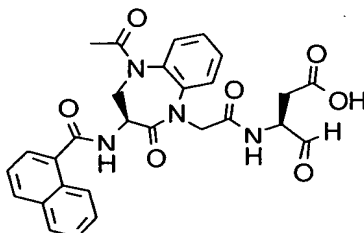
619



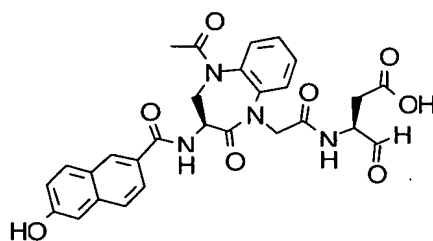
620



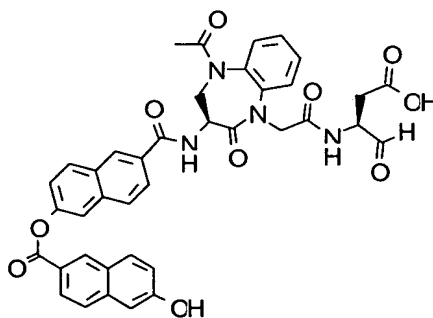
621



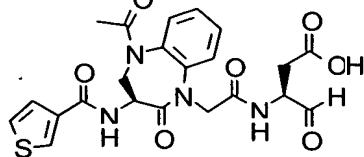
622



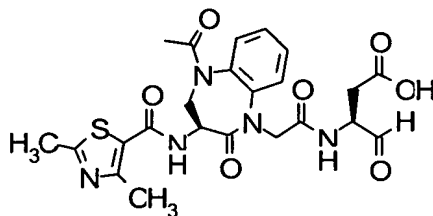
623



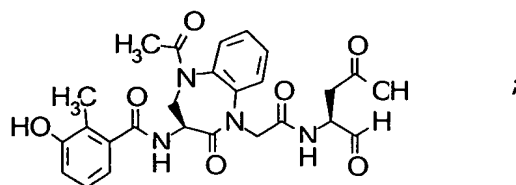
624



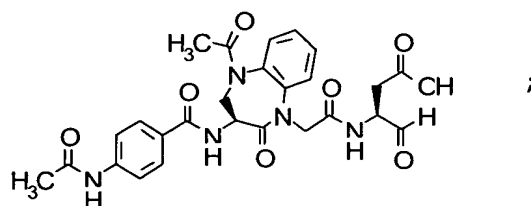
625

 A^{22}

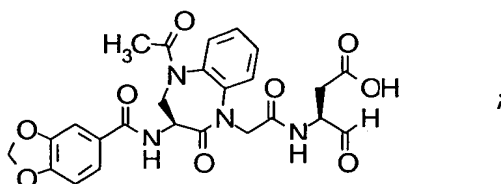
626



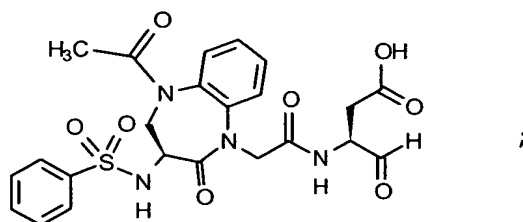
627



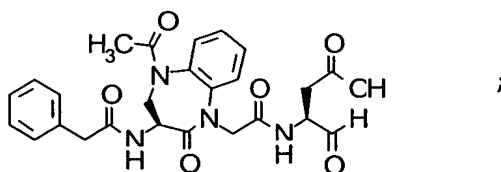
628

A²²

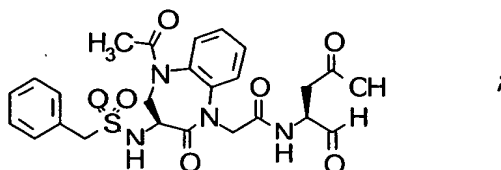
629



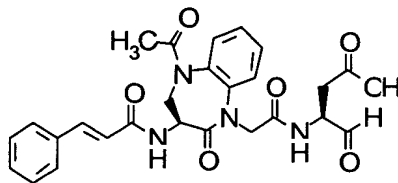
630



631

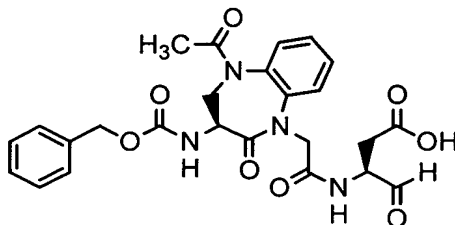


632



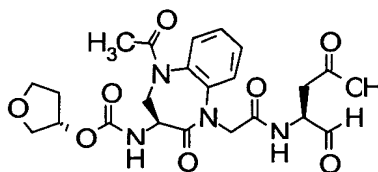
;

633



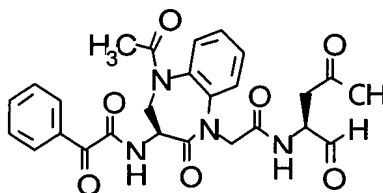
;

634



; and

635

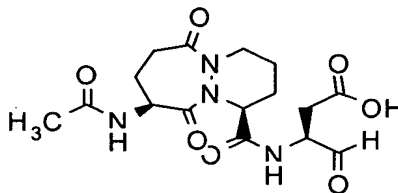


.

A22

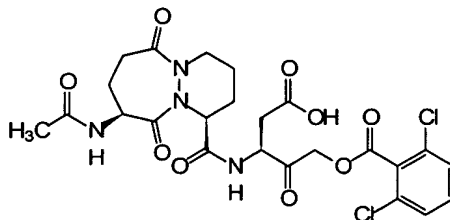
40. The compound according to claims 62 or 68,
selected from the group consisting of:

214c



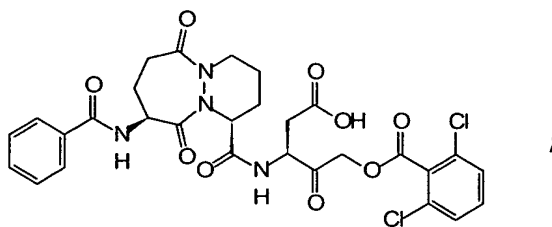
;

217c

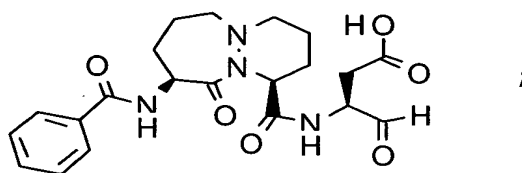


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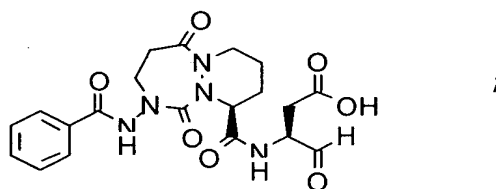
217e



246

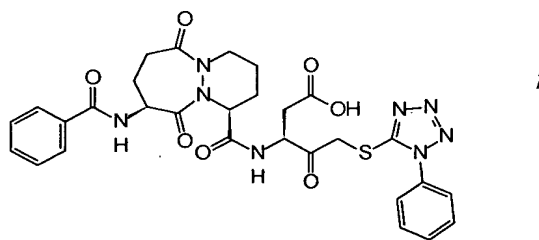


265

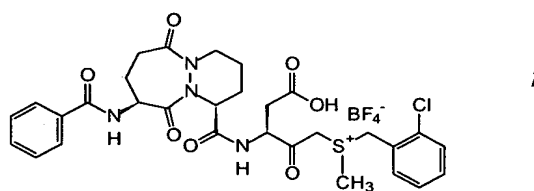


A22

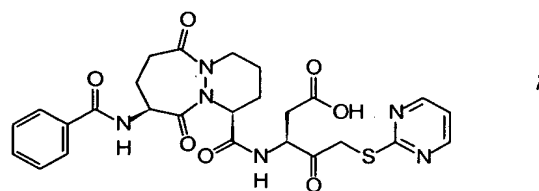
280



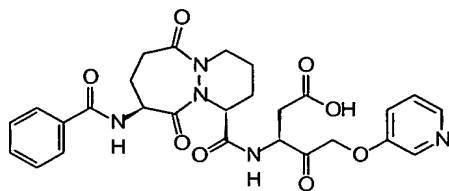
281



282

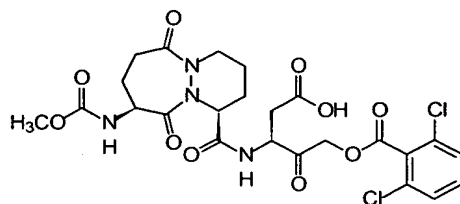


283



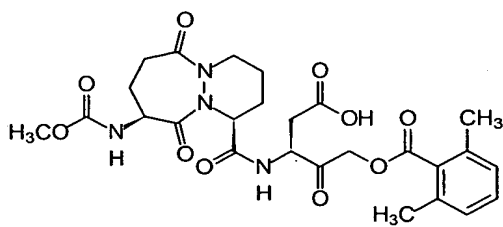
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284



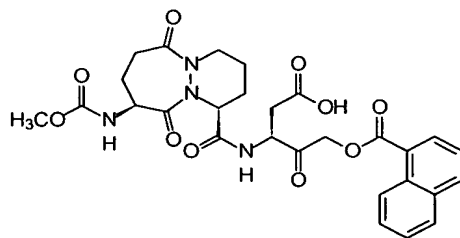
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285



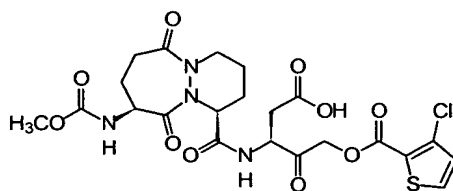
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286



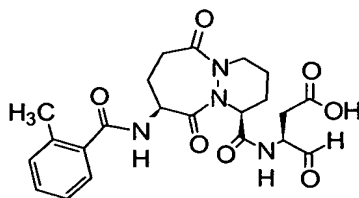
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287



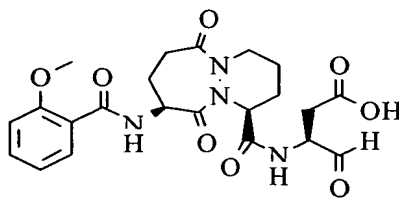
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404



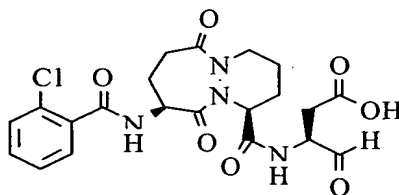
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405



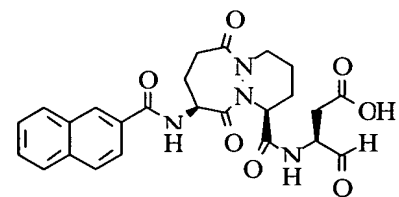
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406



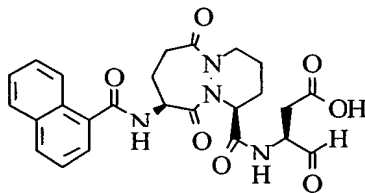
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407



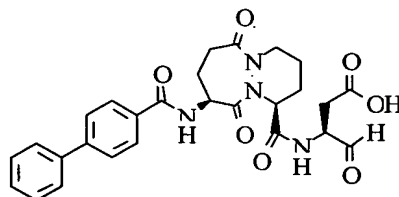
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408



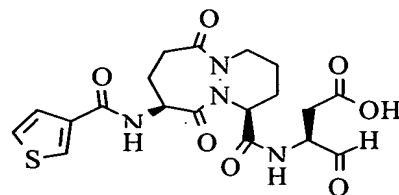
;

409



;

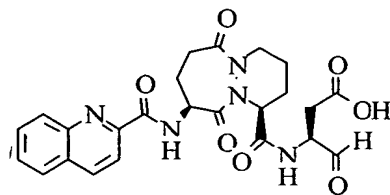
410



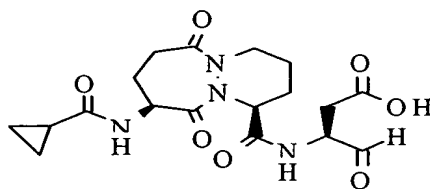
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A22

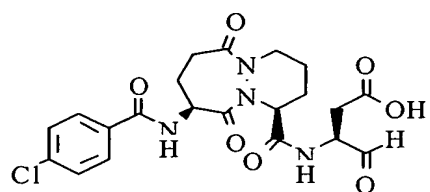
411



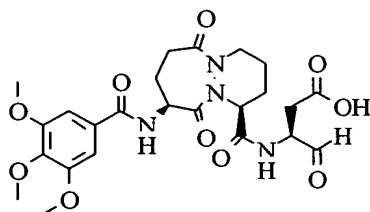
413



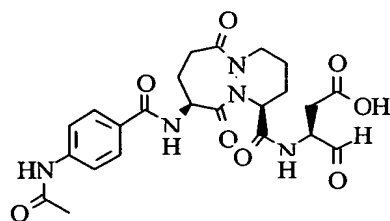
416



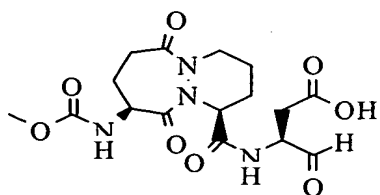
417



418

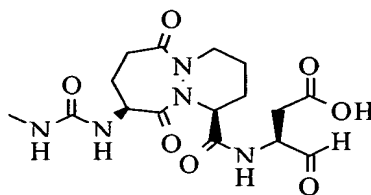


419



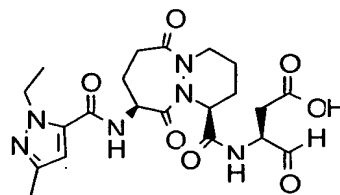
A22

420



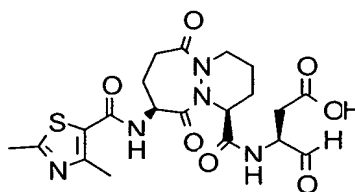
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422



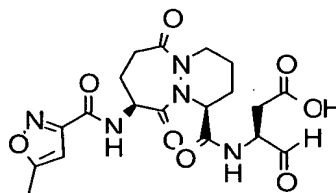
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423



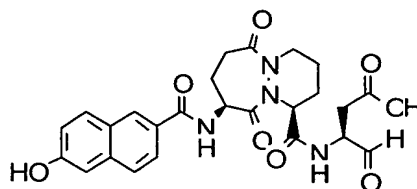
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424



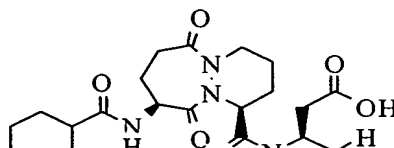
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425



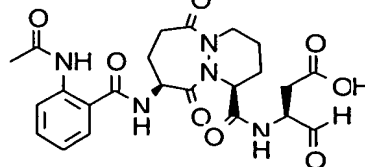
;

426



;

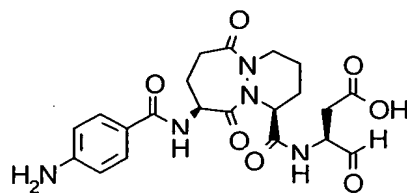
430



;

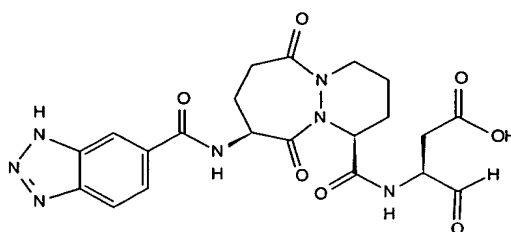
A²²

431



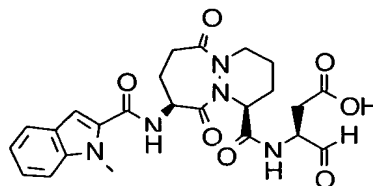
;

432



;

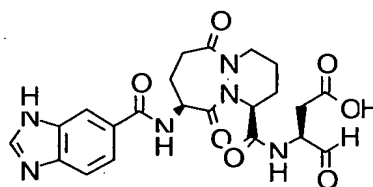
433



;

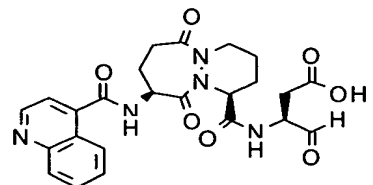
A22

434



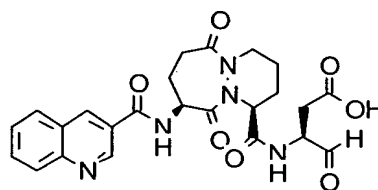
;

435



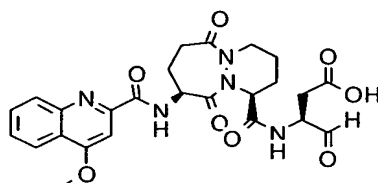
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436



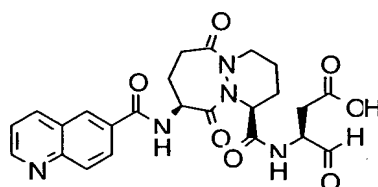
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437



;

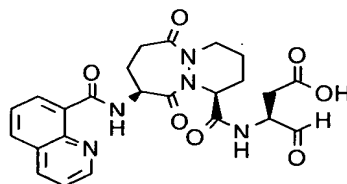
438



;

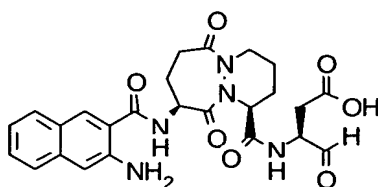
A22

439



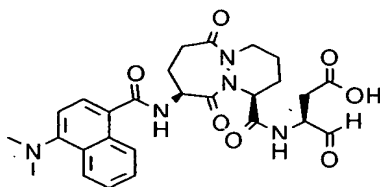
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440



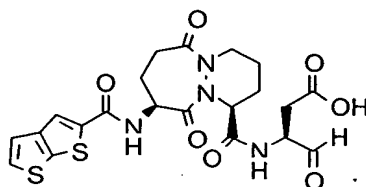
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441



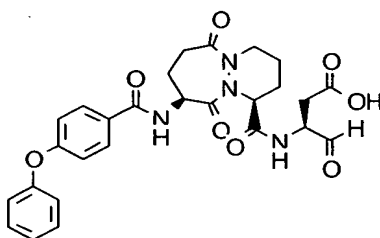
;

442



;

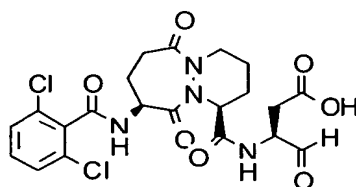
443



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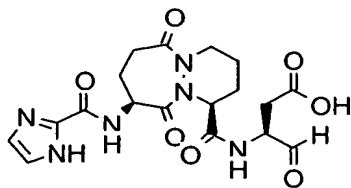
A²²

444



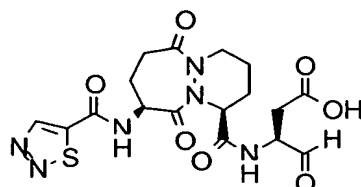
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445



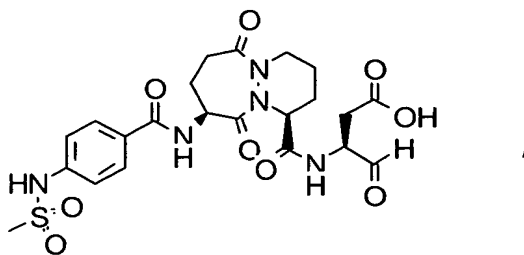
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446

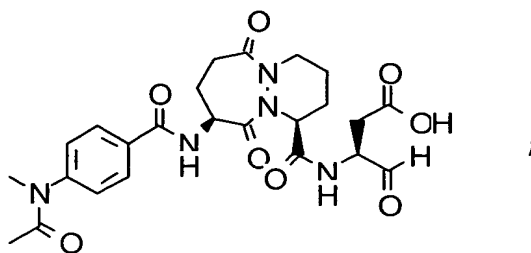


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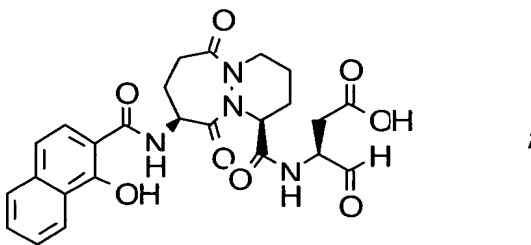
447



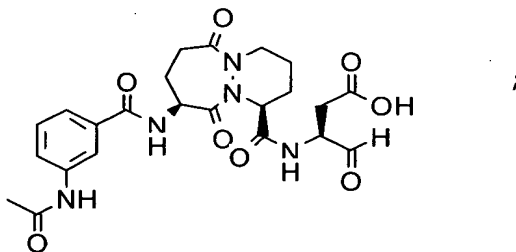
448



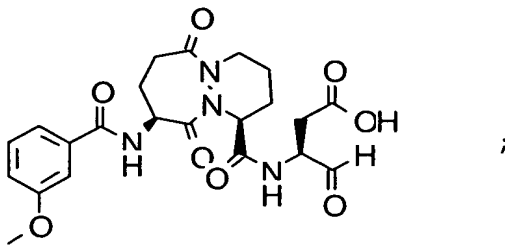
449



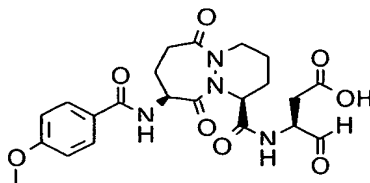
450



451

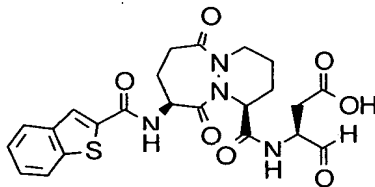


452



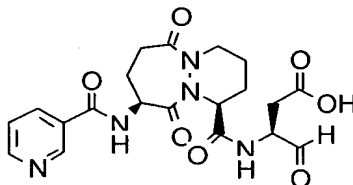
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453



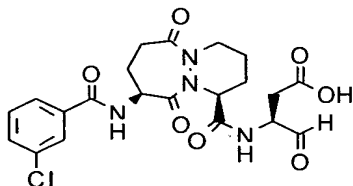
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454



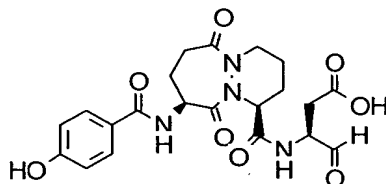
;

455



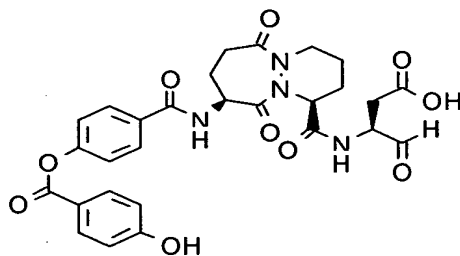
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456



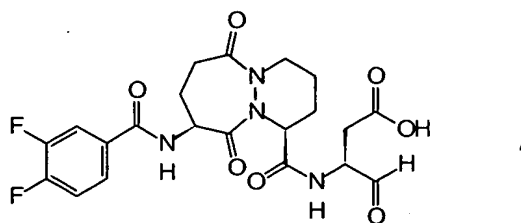
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457

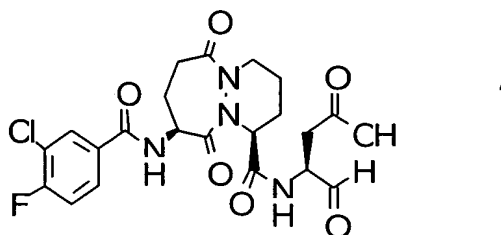


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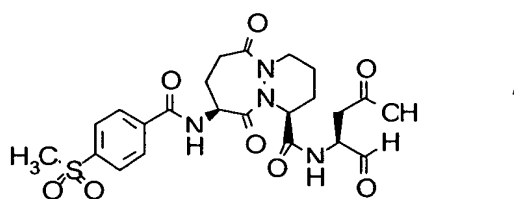
458



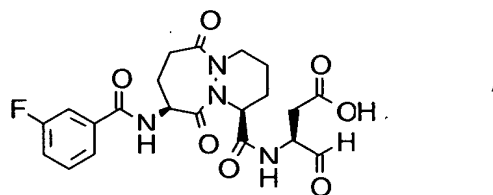
459



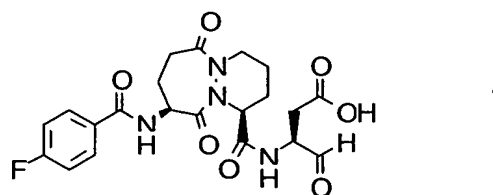
460



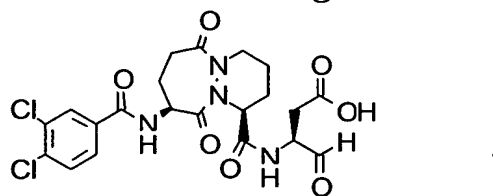
462



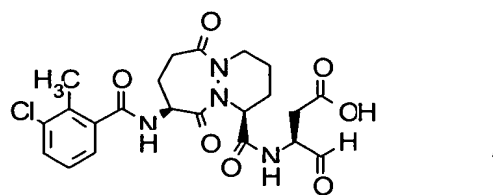
463



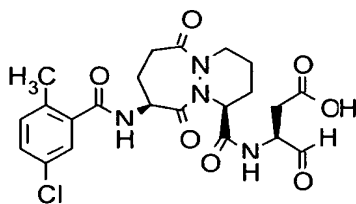
464



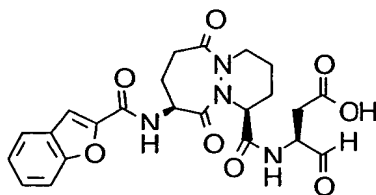
465



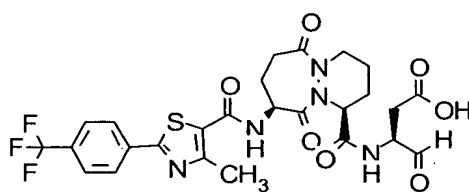
466



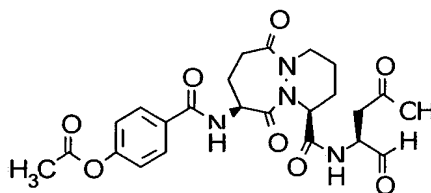
467



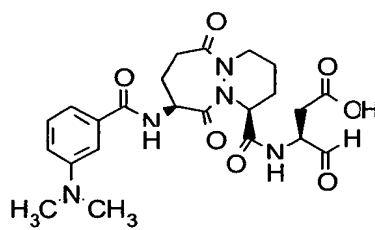
468



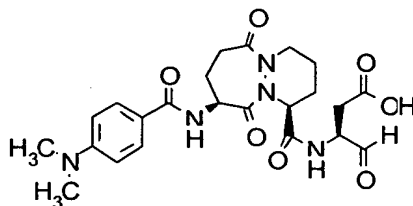
469



470

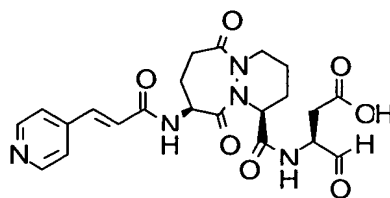


471



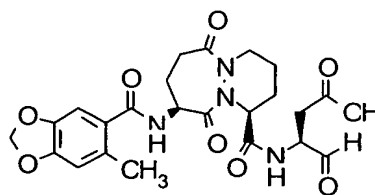
A22

472



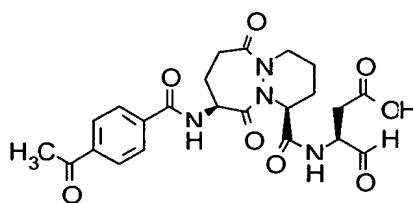
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473



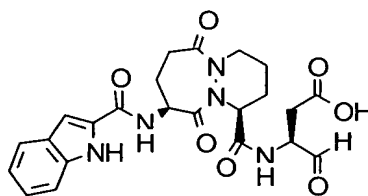
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474



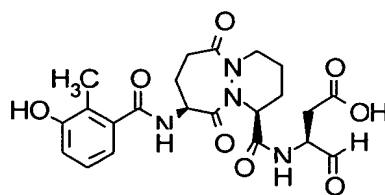
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475



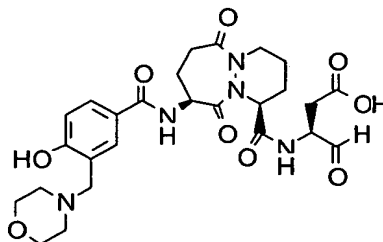
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476



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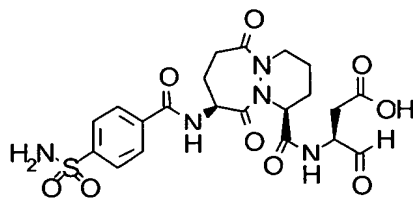
477



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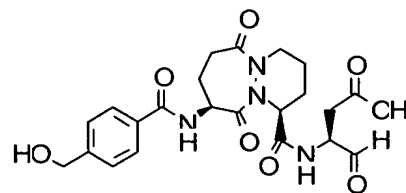
A22

478



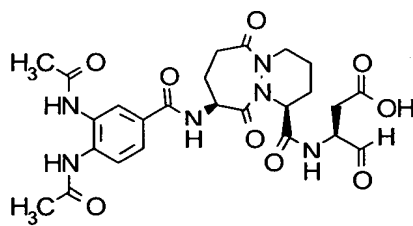
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479



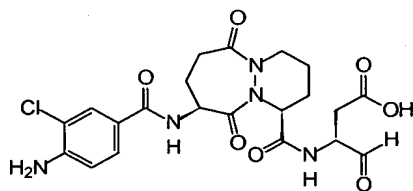
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480



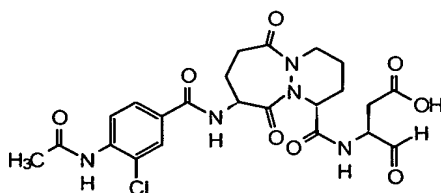
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481



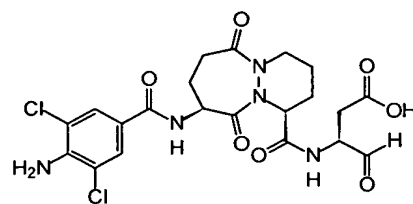
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481s



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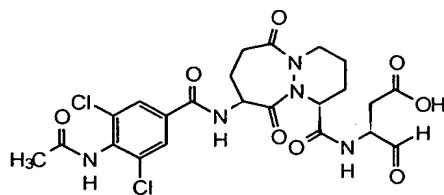
482



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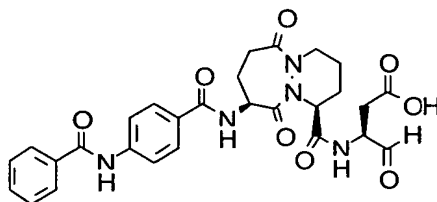
A²²

482s



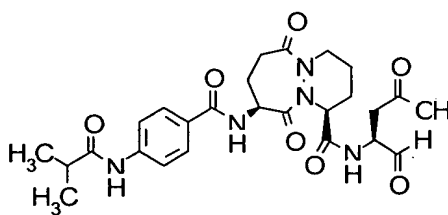
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483



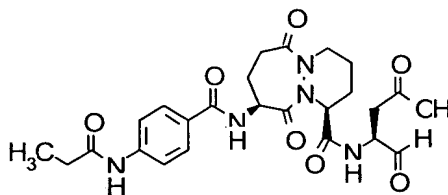
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484



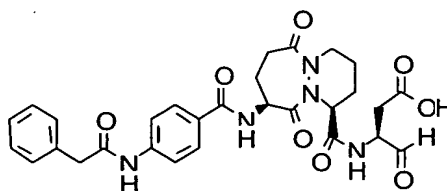
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485



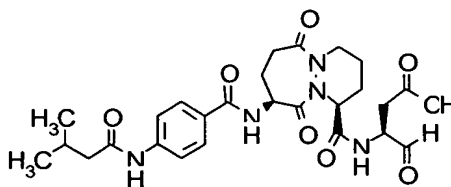
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486



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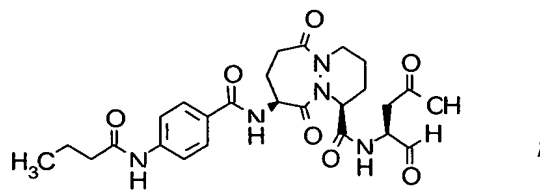
487



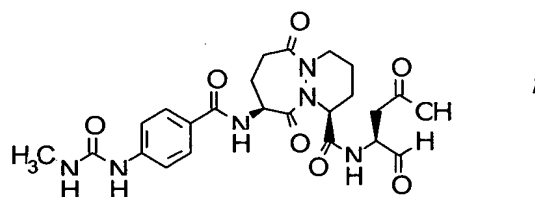
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A22

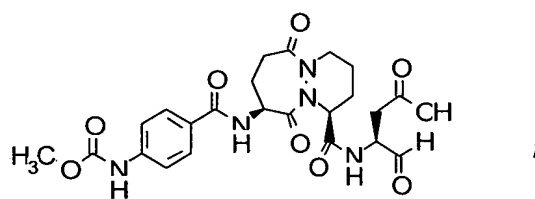
488



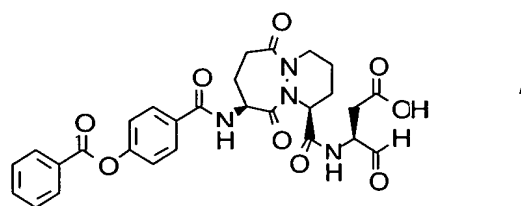
489



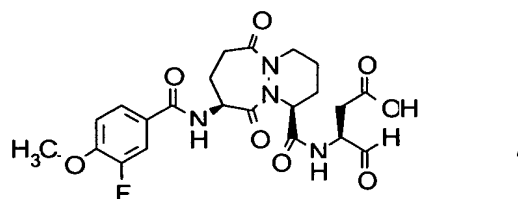
490



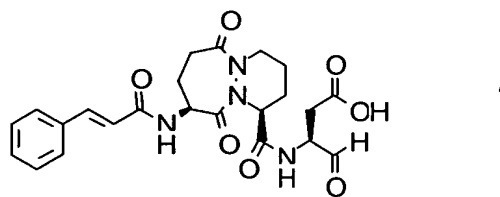
491



493

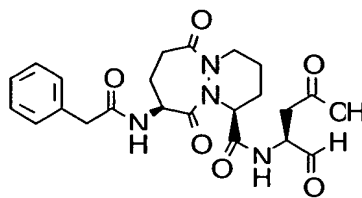


494



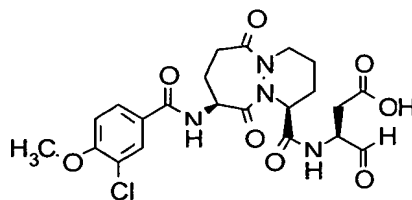
A22

495



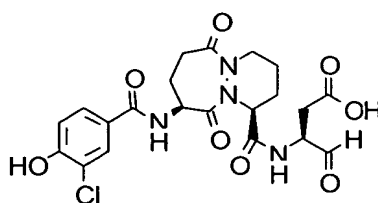
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497



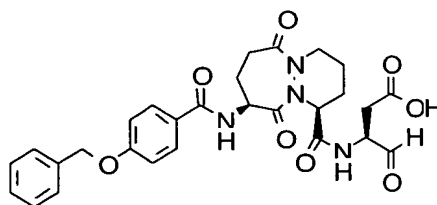
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498



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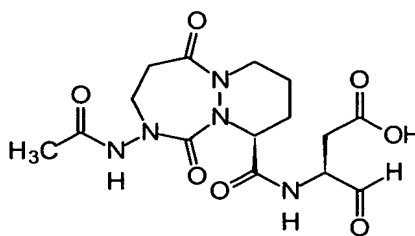
499



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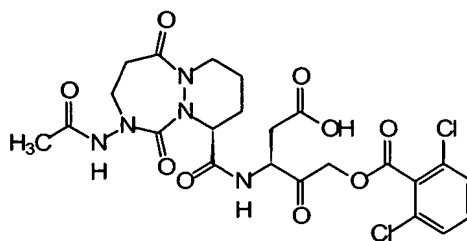
A²²

814c



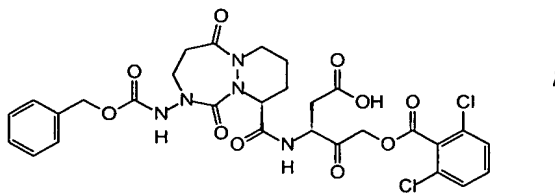
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817c

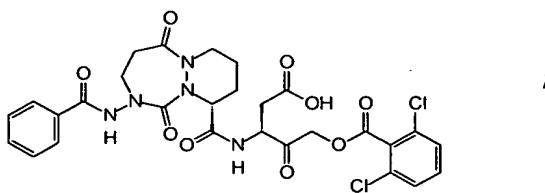


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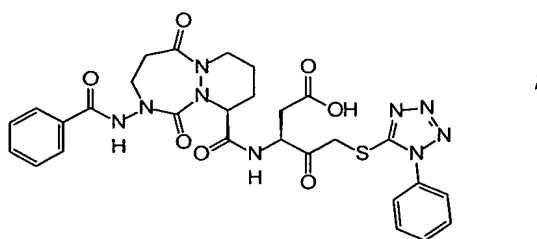
817d



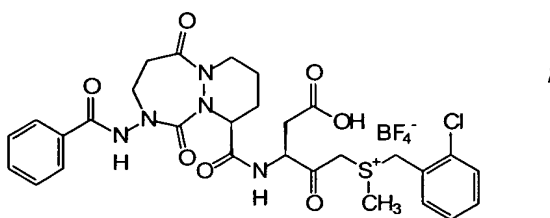
817e



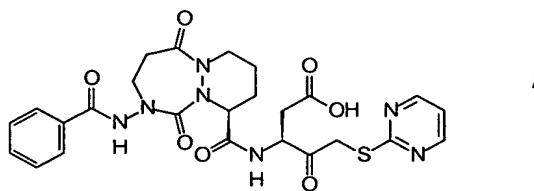
880



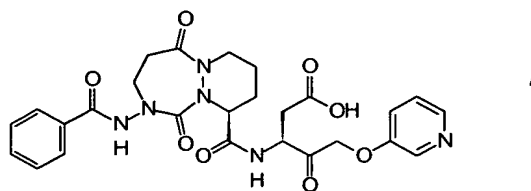
881



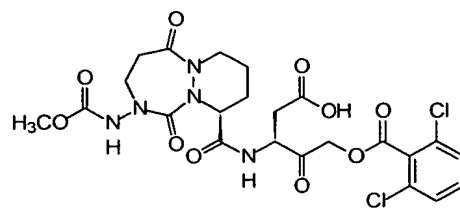
882



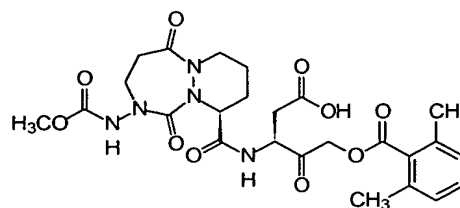
883



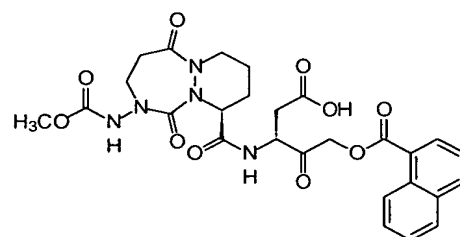
884



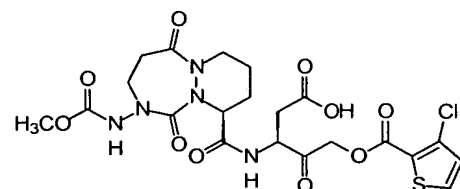
885



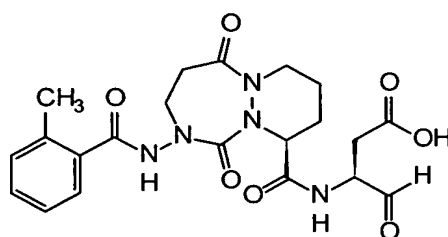
886



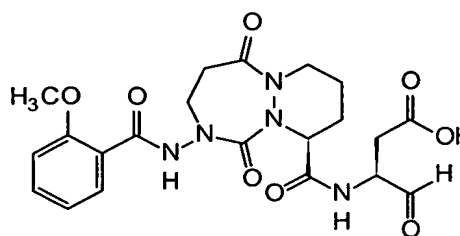
887



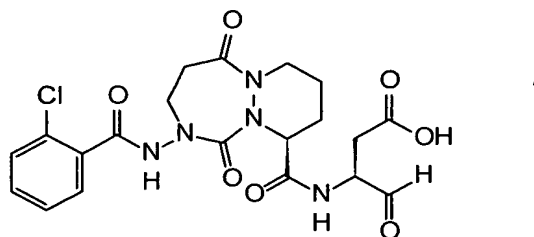
1004



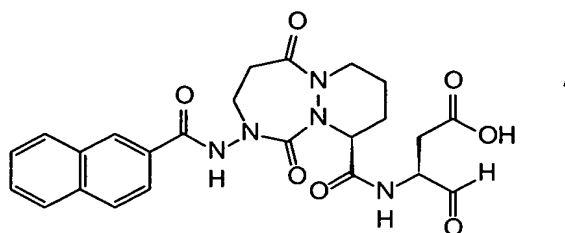
1005



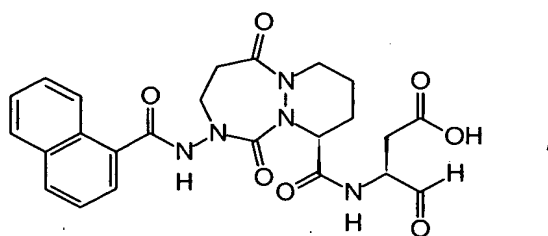
1006



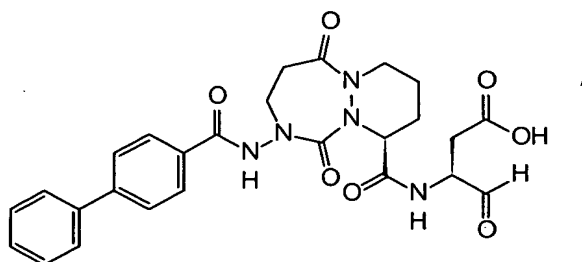
1007



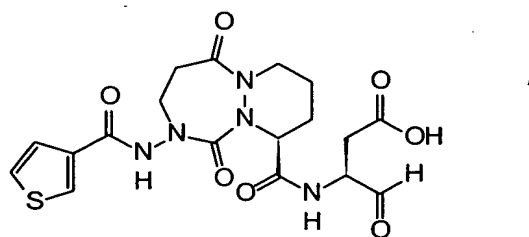
1008



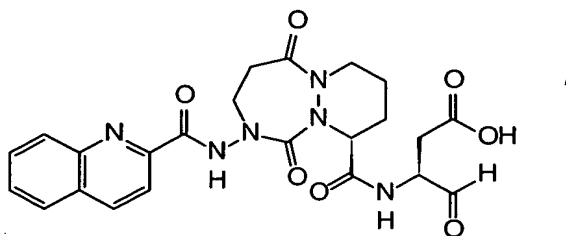
1009



1010

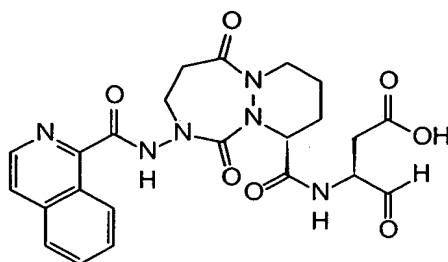


1011



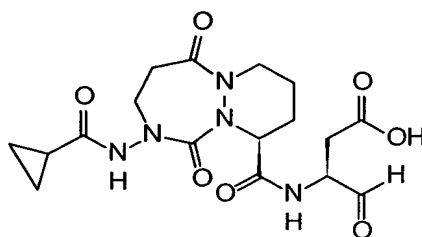
A22

1012



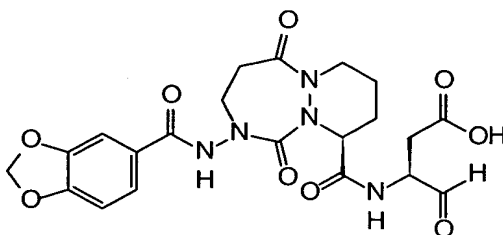
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1013



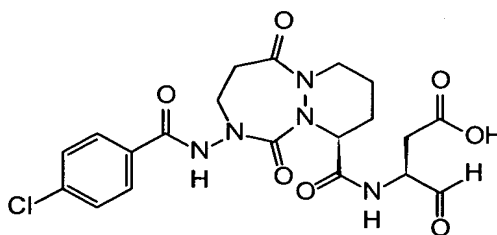
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1015



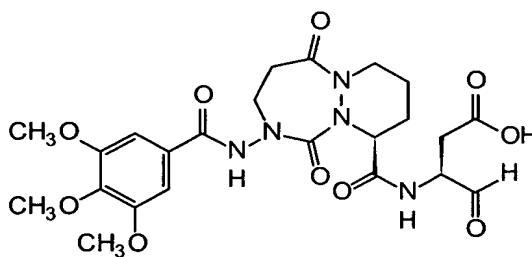
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1016



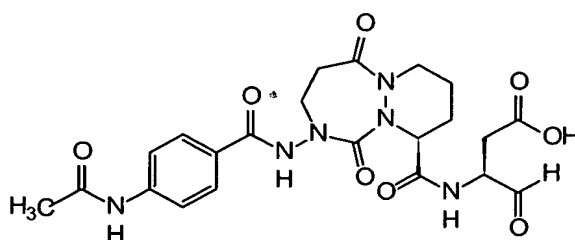
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1017



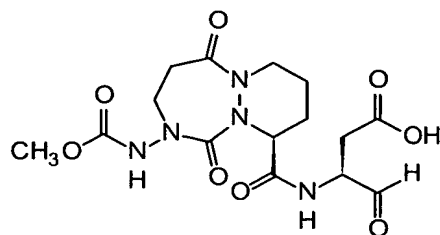
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1018

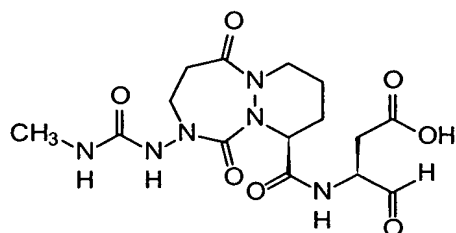


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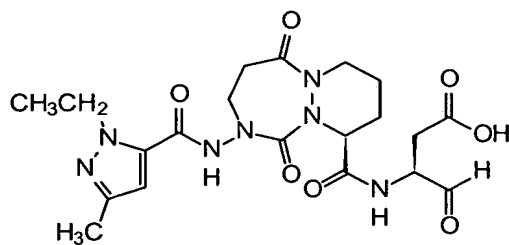
1019



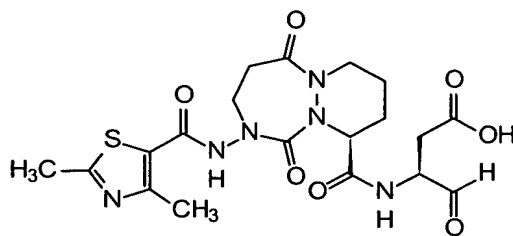
1020



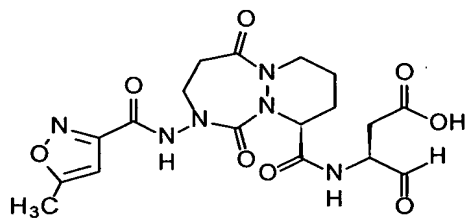
1022



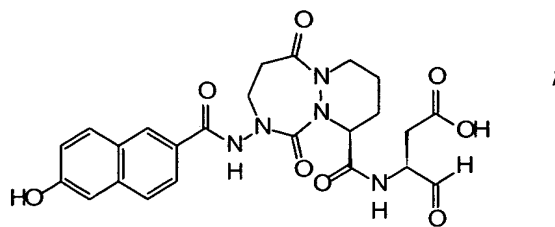
1023



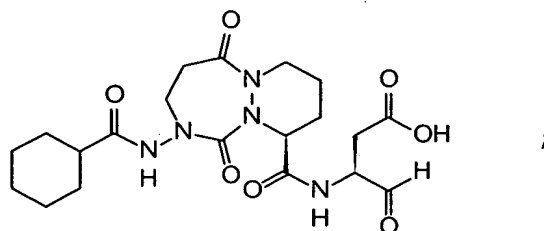
1024



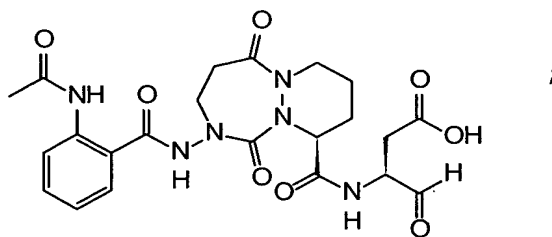
1025



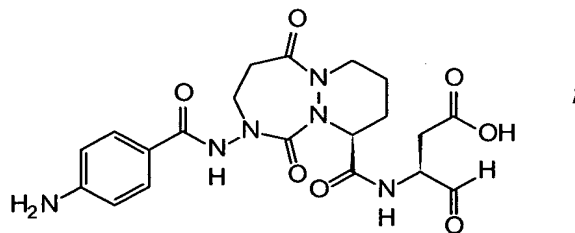
1026



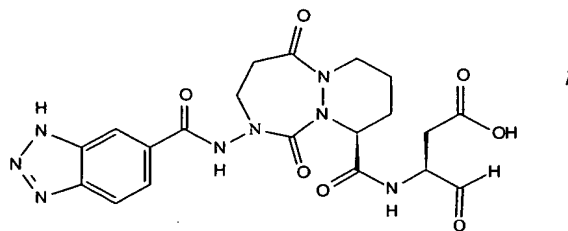
1030

A²²

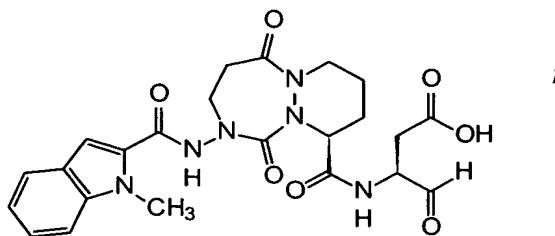
1031



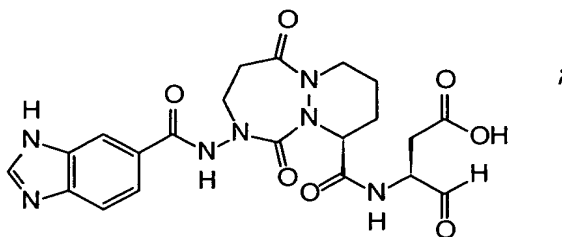
1032



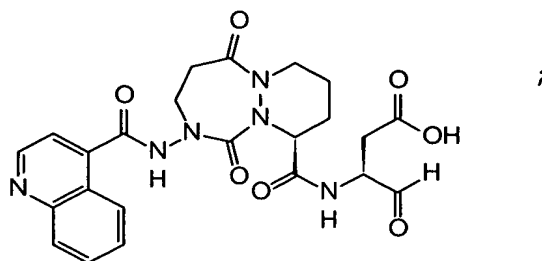
1033



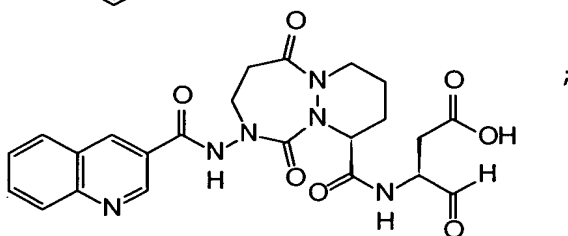
1034



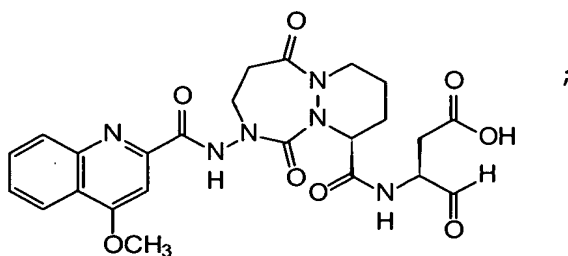
1035



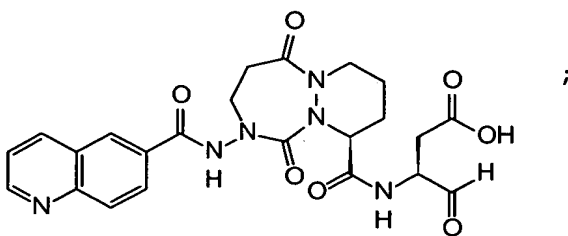
1036



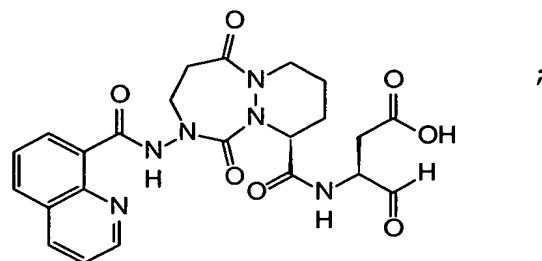
1037



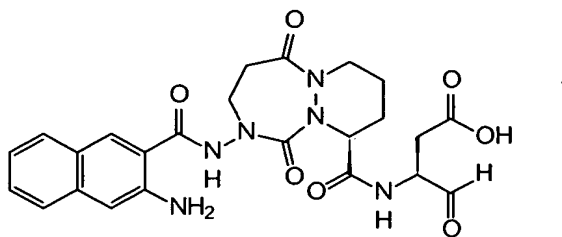
1038



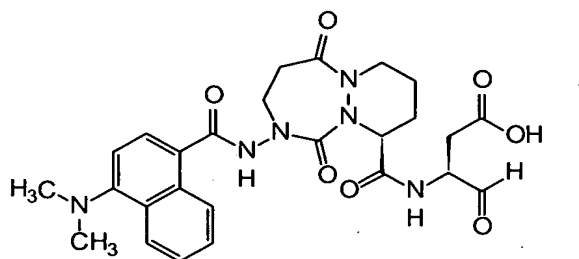
1039



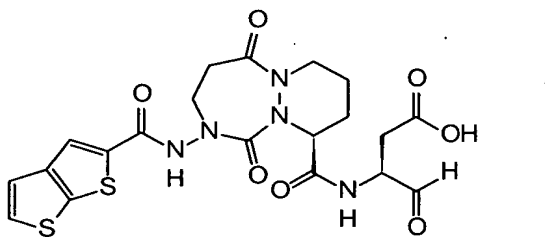
1040



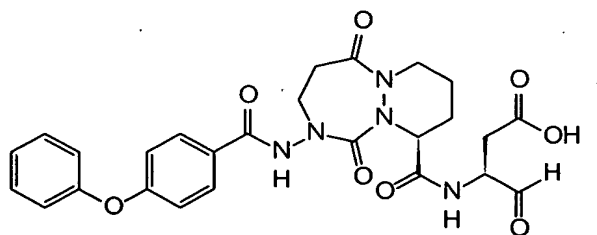
1041



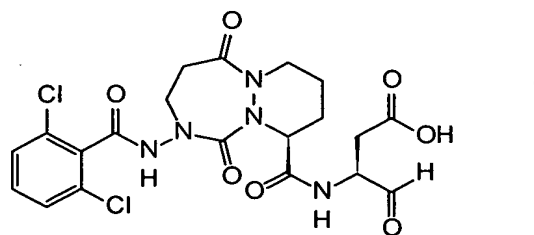
1042



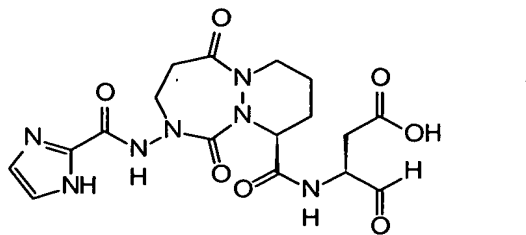
1043



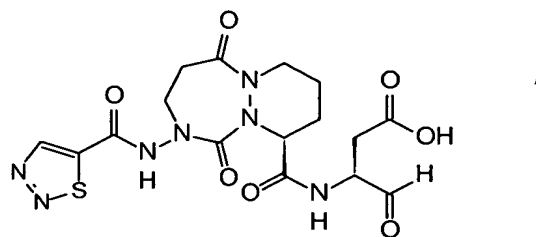
1044



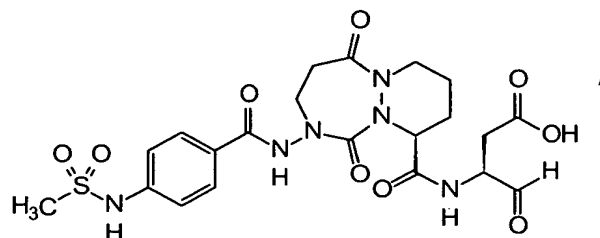
1045



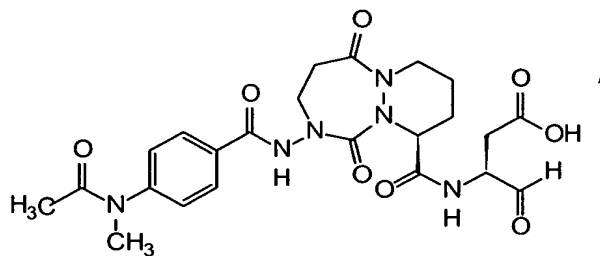
1046



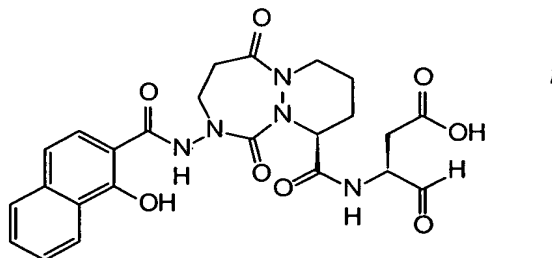
1047



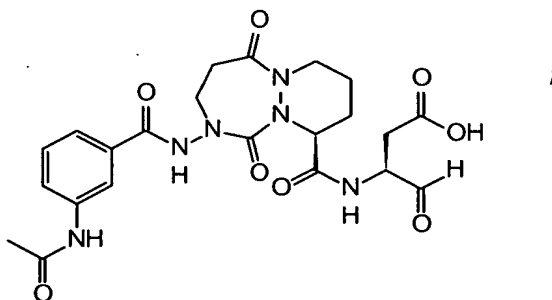
1048

A²²

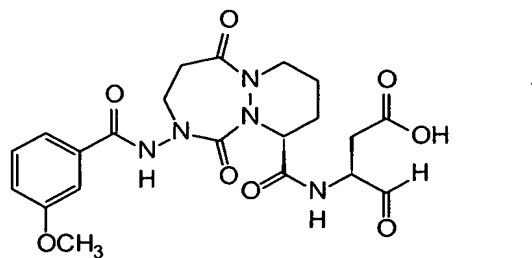
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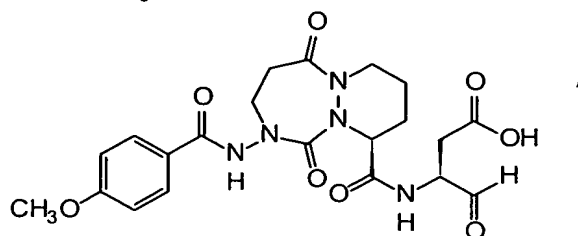
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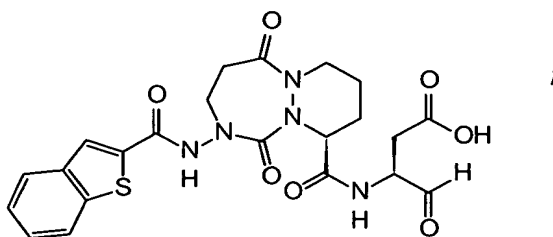
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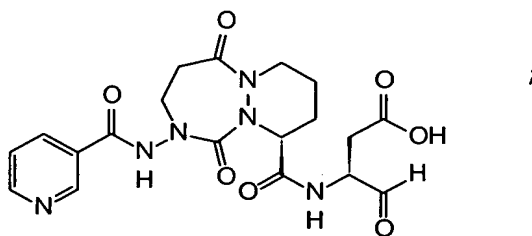
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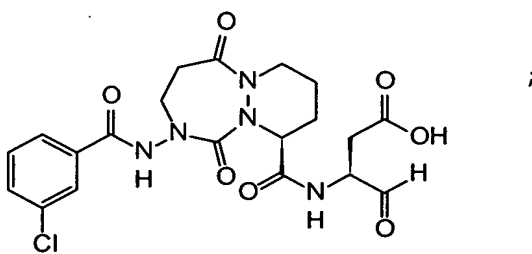
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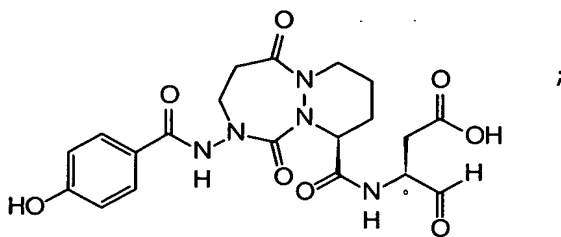
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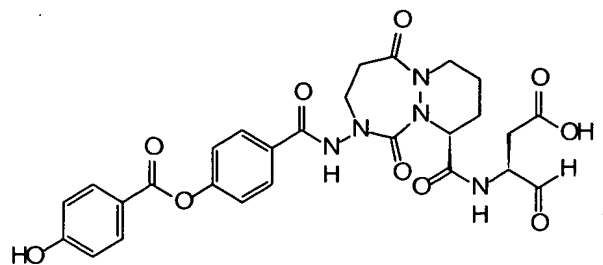
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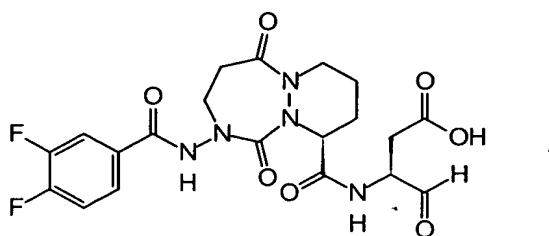
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A²²

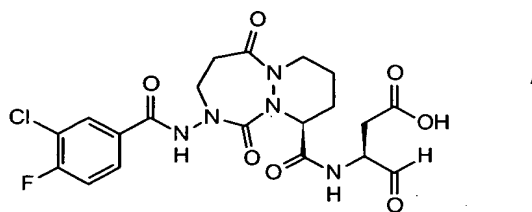
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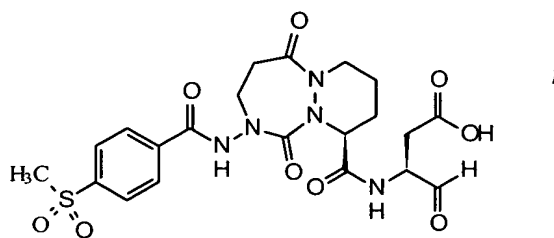
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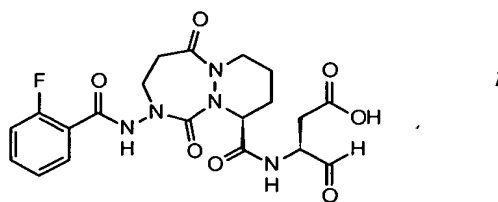
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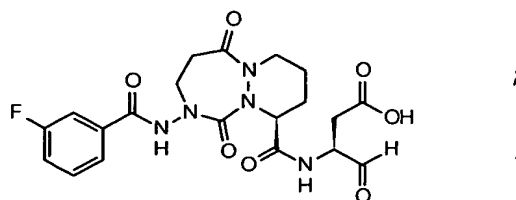
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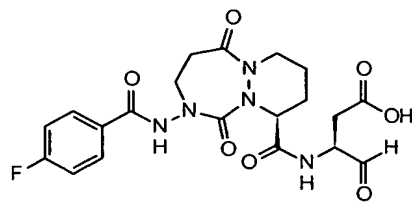
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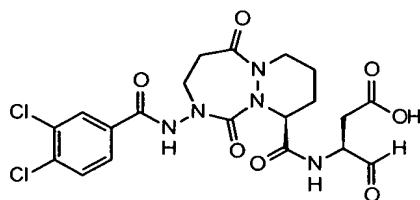
A²²

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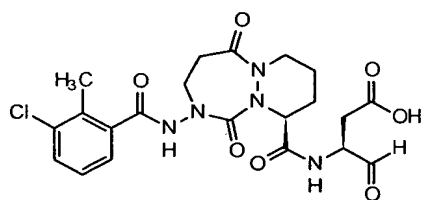
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1064



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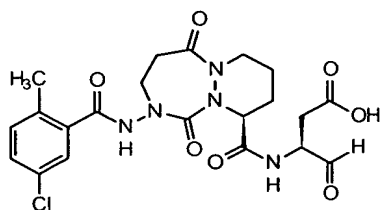
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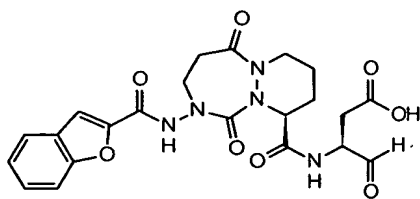
A²²

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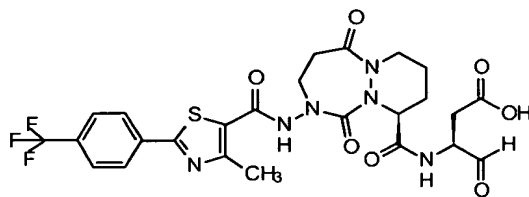
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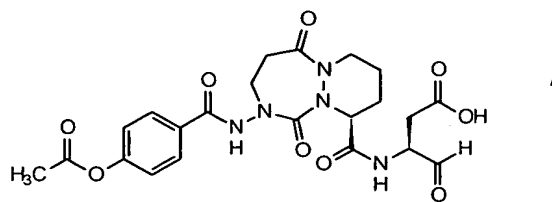
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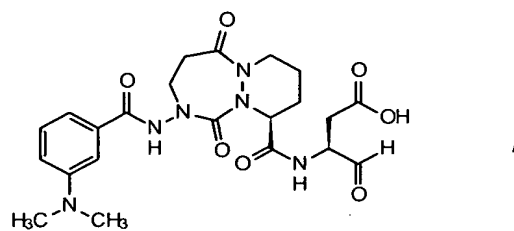


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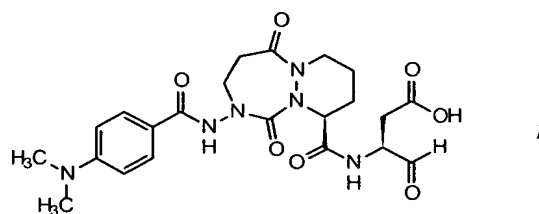
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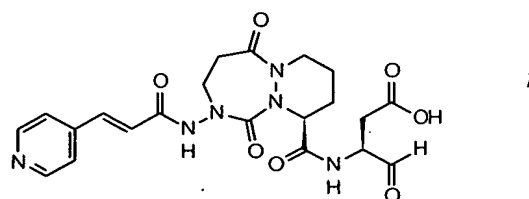
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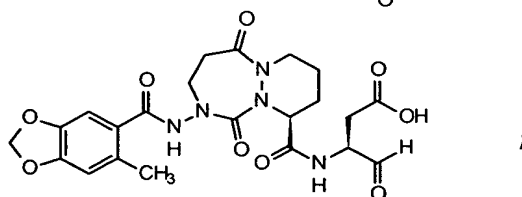
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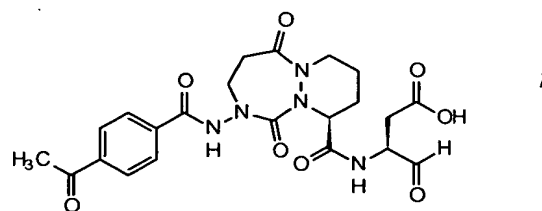
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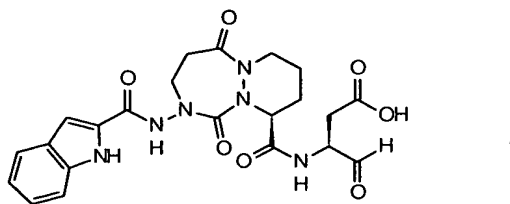
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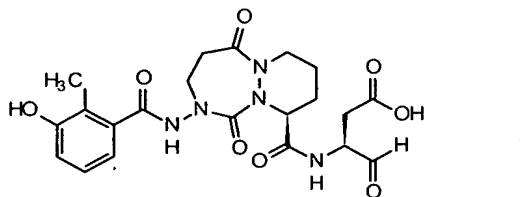
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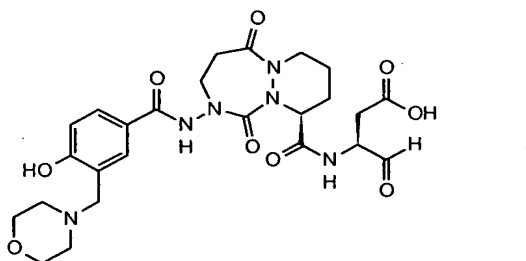
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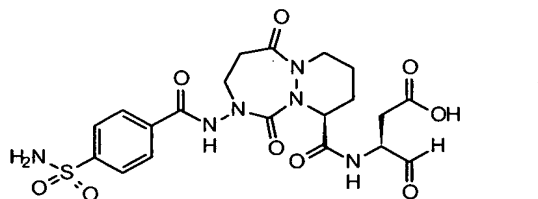
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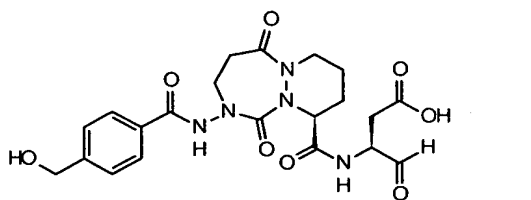
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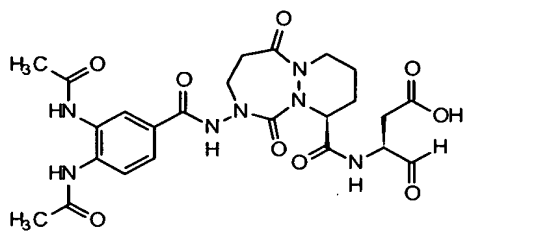
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1079

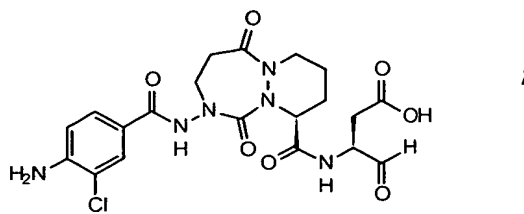


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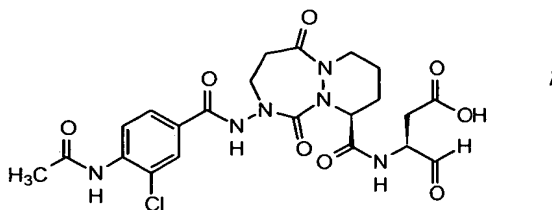


A22

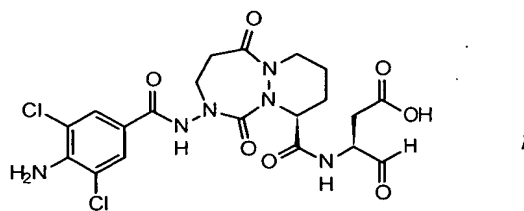
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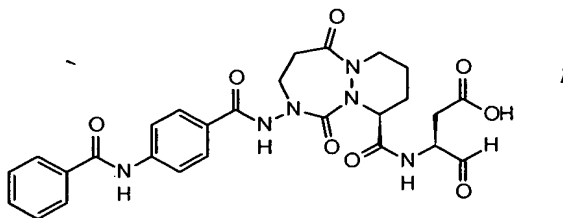
1081s



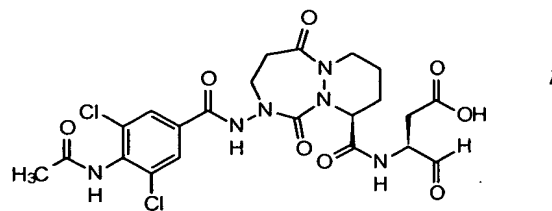
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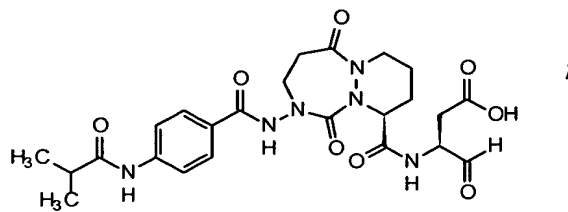
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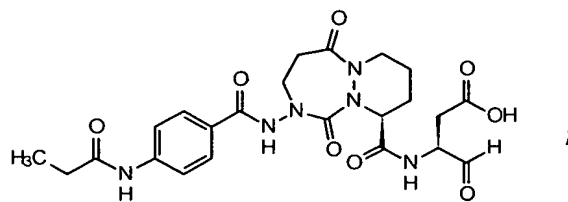
1082s



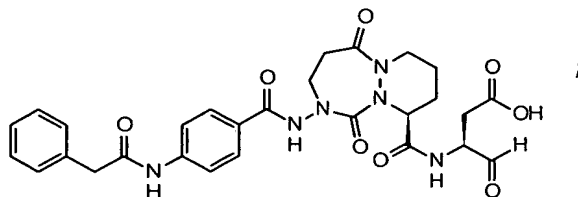
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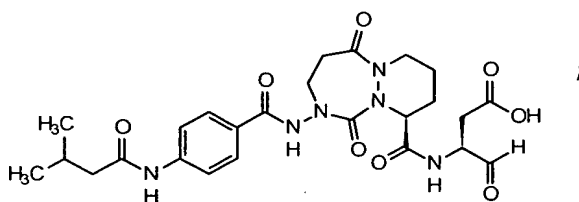
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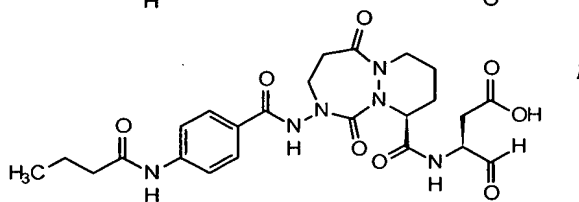
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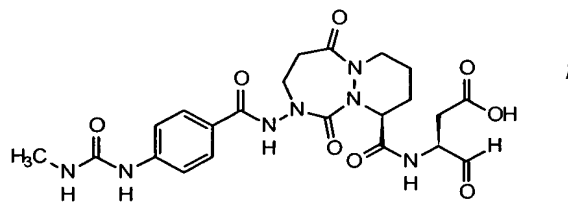
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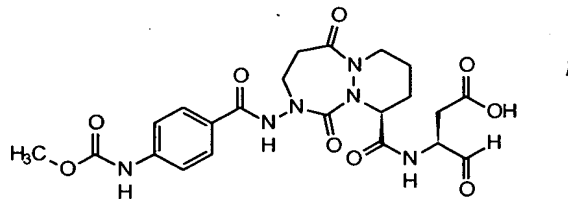
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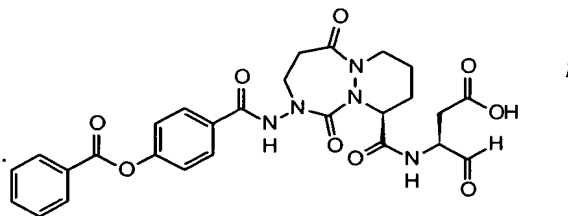
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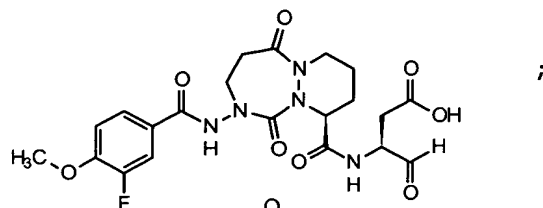
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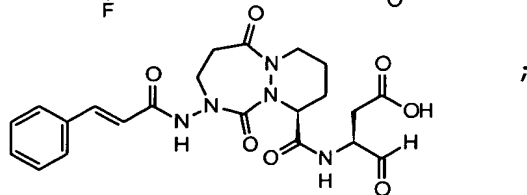
1091

A²²

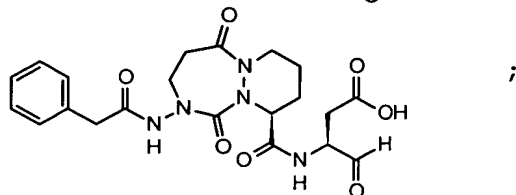
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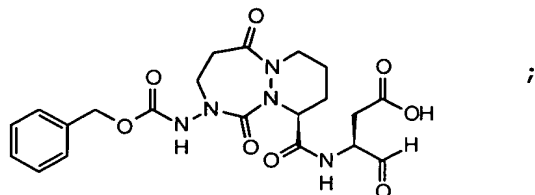
1094



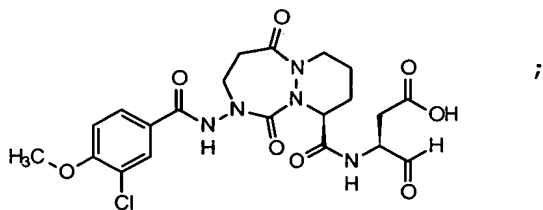
1095



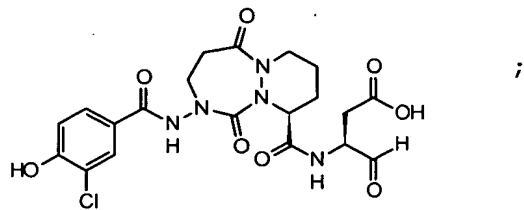
1096

A²²

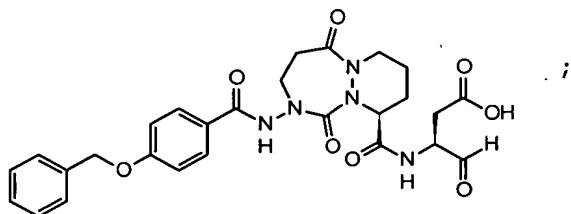
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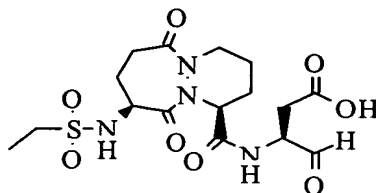
1098



1099

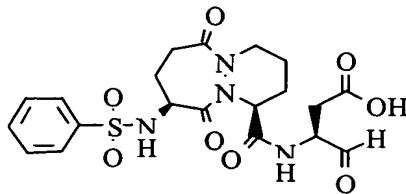


421



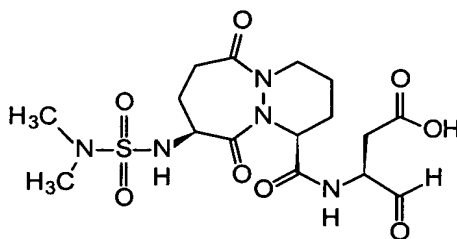
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427



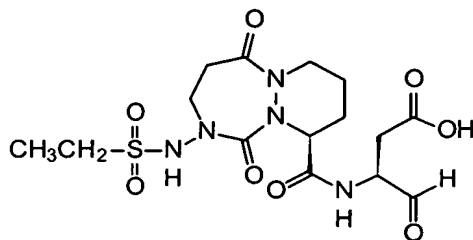
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428



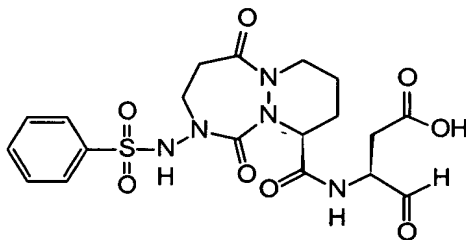
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1021



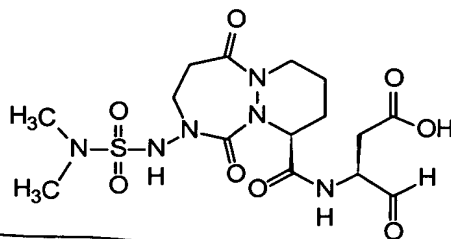
;

1027



; and

1028



.

42. A pharmaceutical composition comprising a

compound according to any one of claims 38-40, 57, 62, 66, 68, 79-83, 88-93, 104, 112, 114, 118-131, 133-135 and a pharmaceutically acceptable carrier.

A24 55. A method for treating or preventing a disease selected from the group consisting of an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke in a patient comprising the step of administering to said patient a pharmaceutical composition according to claim 42.

A25 88. The compound according to claim 80, wherein R_5 is $-C(O)-R_{10}$ or $-C(O)-C(O)-R_{10}$.

A26

118. The compound according to claims 104 or 114, wherein R_5 is $-C(O)-R_{10}$ or $-C(O)C(O)-R_{10}$.

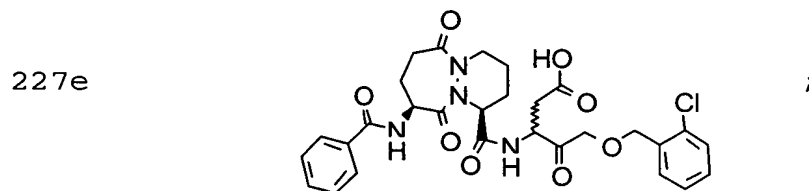
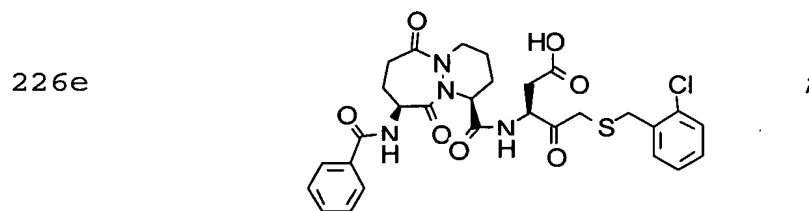
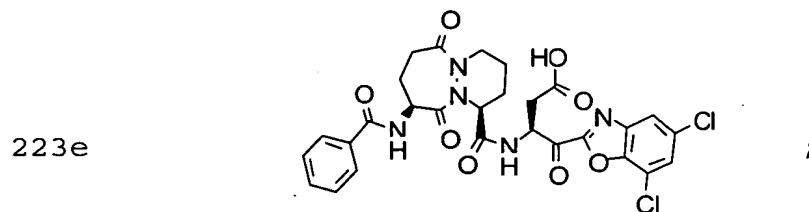
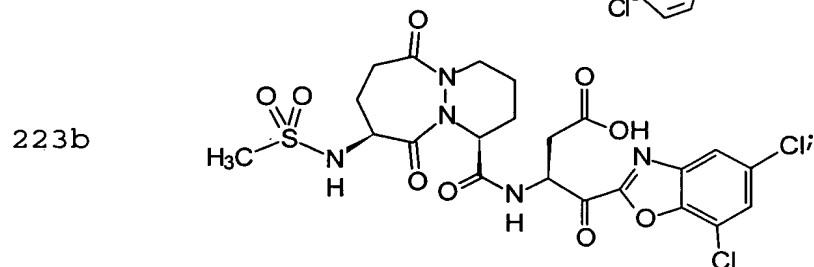
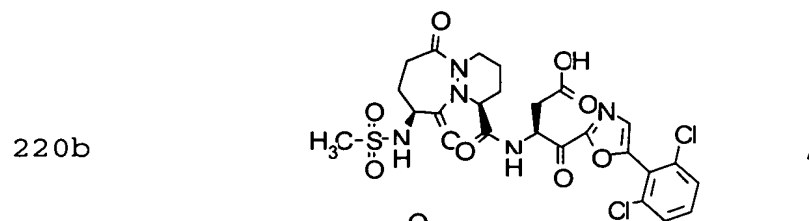
A27

138. A method for treating or preventing a disease selected from an IGIF mediated disease, an IFN- γ mediated disease, an inflammatory disease, an autoimmune disease, an infectious disease, a proliferative disease, a neurodegenerative disease, a necrotic disease, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia, adult respiratory distress syndrome, infectious hepatitis, sepsis, septic shock, Shigellosis, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome comprising the step of administering to said patient a pharmaceutical composition according to claim 42.

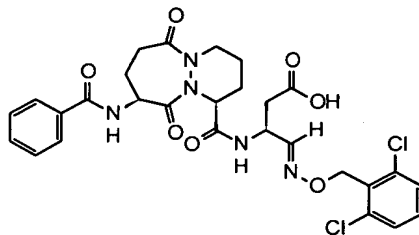
APPENDIX 4

Amended Claims Marked to Show Amendments

38. The compound according to claims [8] 62 or 68, selected from the group consisting of:

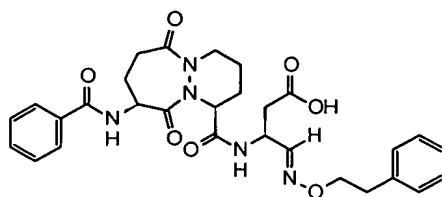


307a



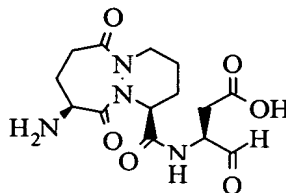
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307b



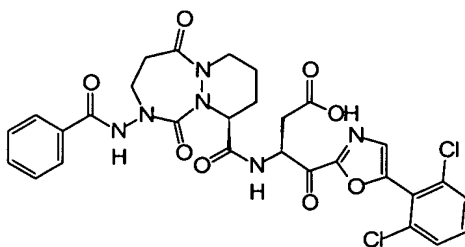
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429



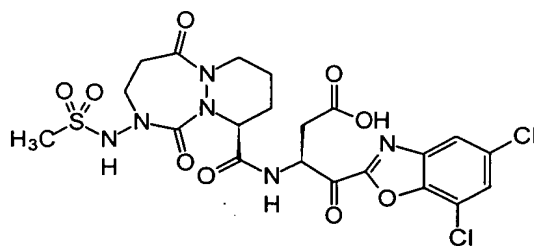
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820b



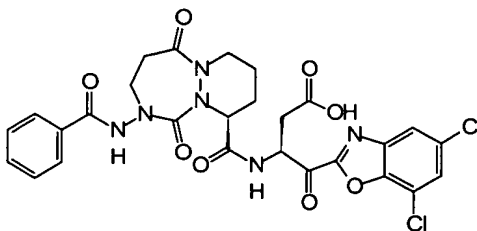
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823b



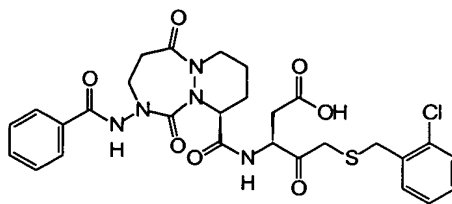
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823e



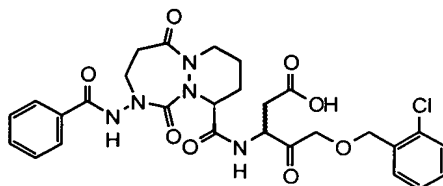
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826e



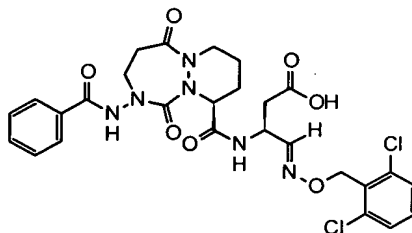
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827e



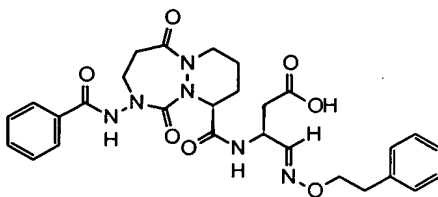
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907a



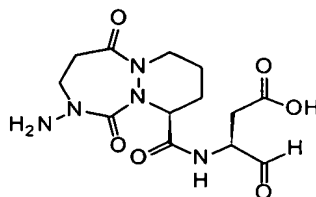
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907b



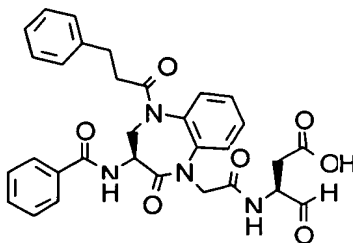
; and

1029



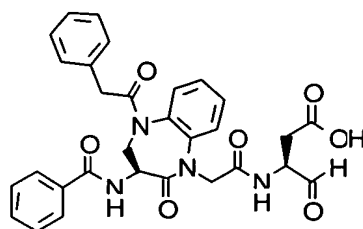
39. The compound according to claim [15] 62,
selected from the group consisting of:

605a



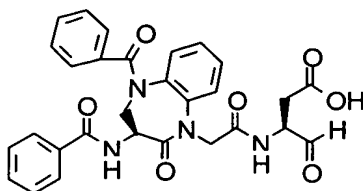
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605b



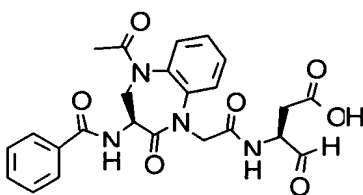
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605c



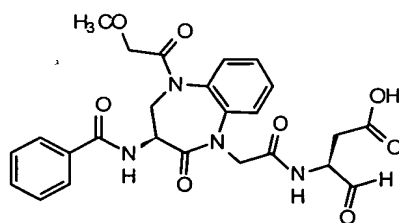
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605d



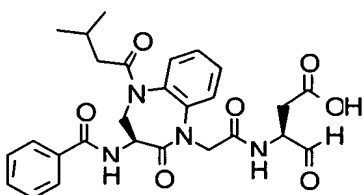
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605e



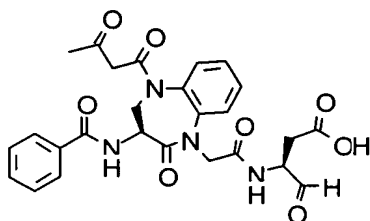
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605f



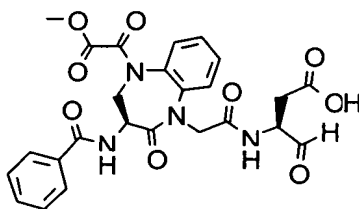
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605g



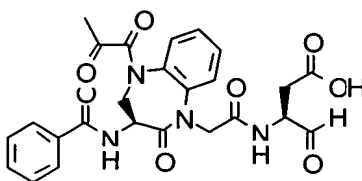
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605h



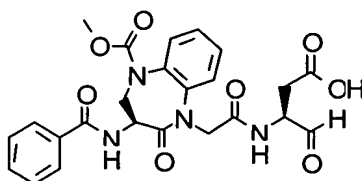
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605i



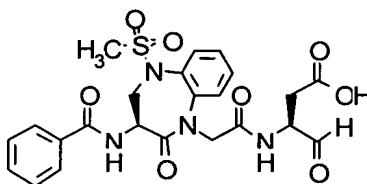
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605j



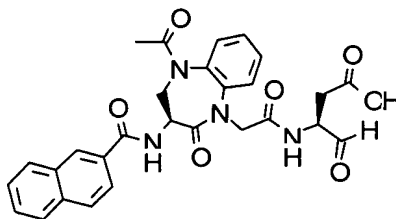
;

605m



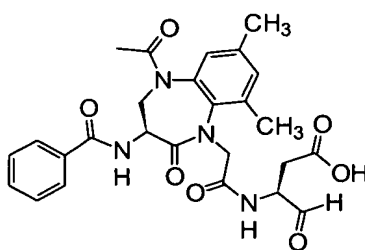
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605n



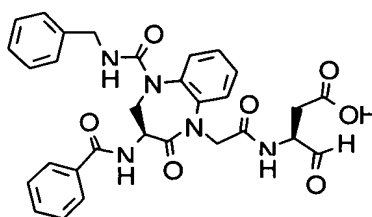
;

605o



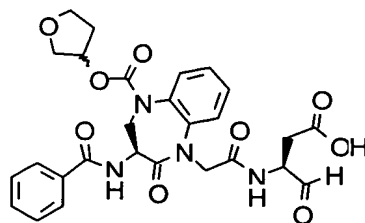
;

605p



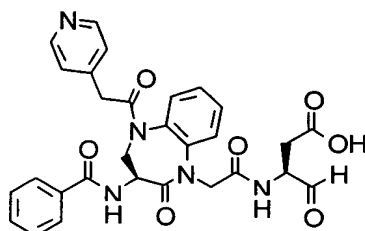
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605q



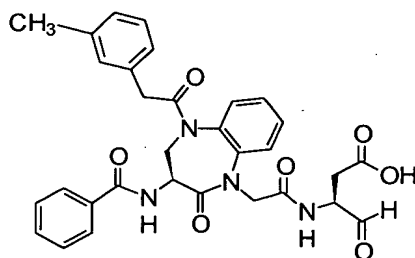
;

605s



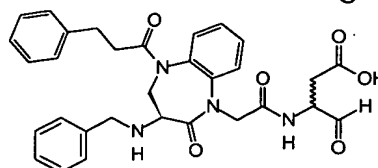
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605t



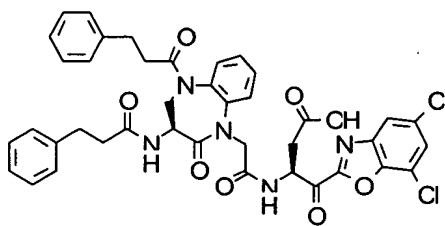
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605v



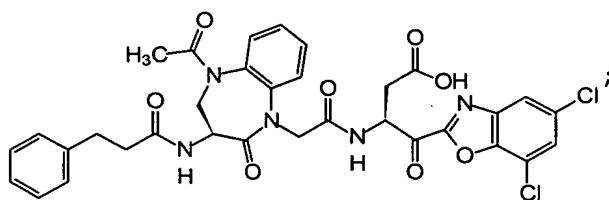
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609a

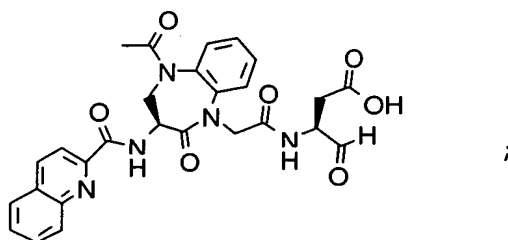


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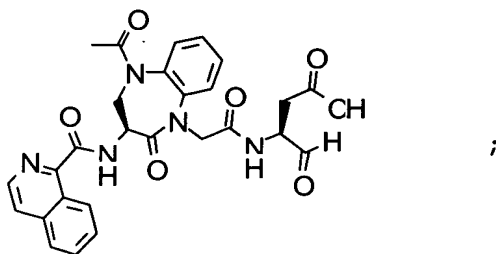
609b



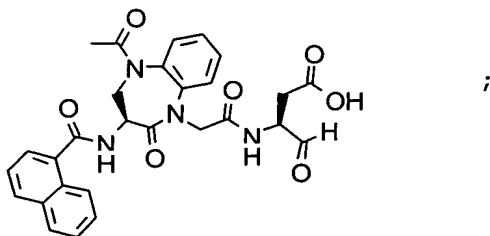
619



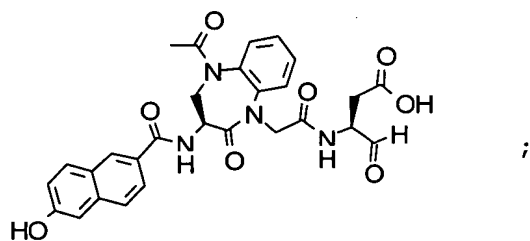
620



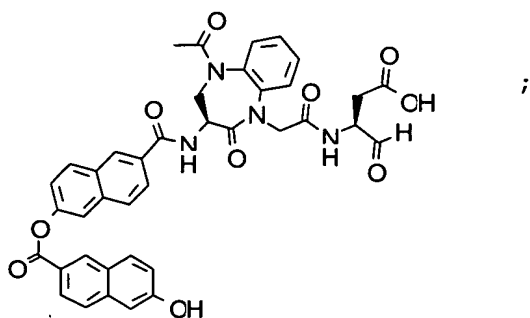
621



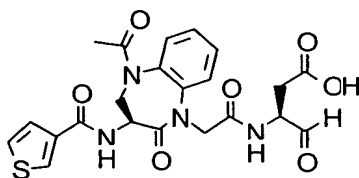
622



623

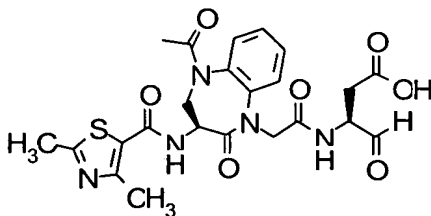


624



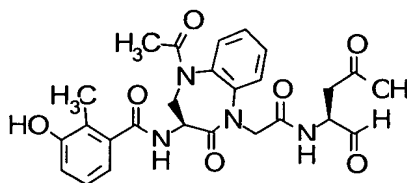
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625



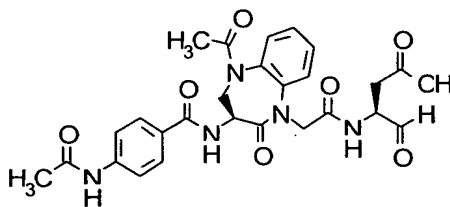
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626



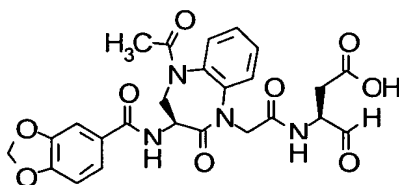
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627



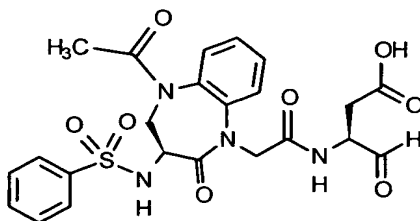
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628



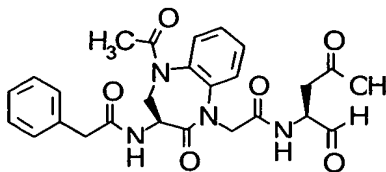
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629



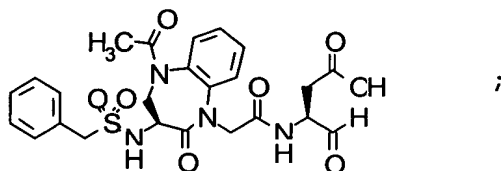
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630



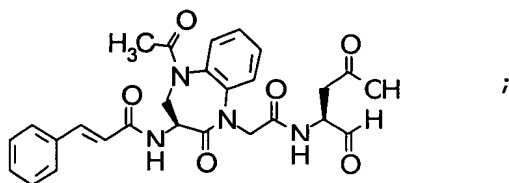
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631



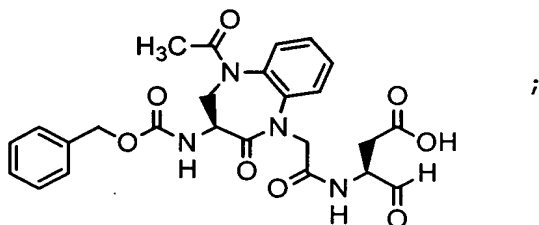
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632



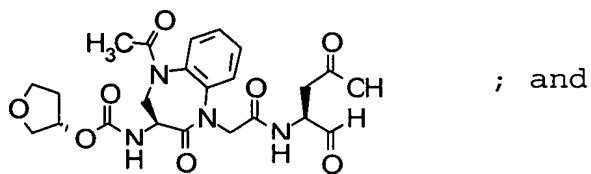
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633



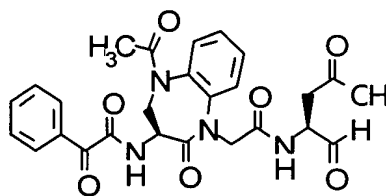
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634



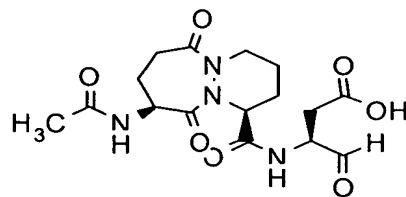
; and

635



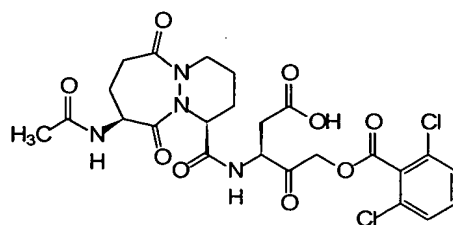
40. The compound according to claims [8] 62 or 68, selected from the group consisting of:

214c



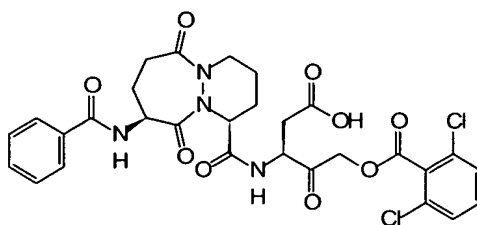
;

217c



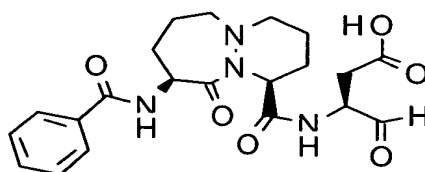
;

217e



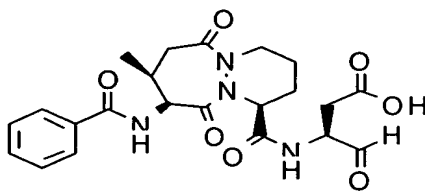
;

246



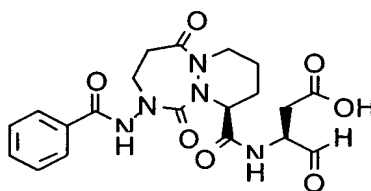
;

[257



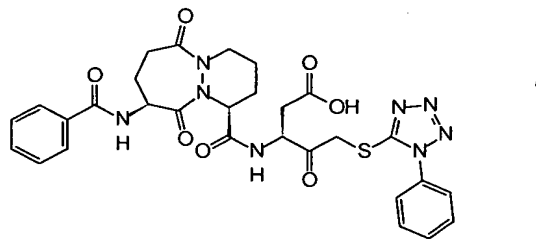
;]

265

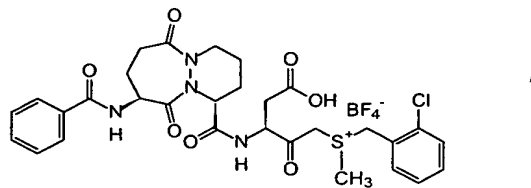


;

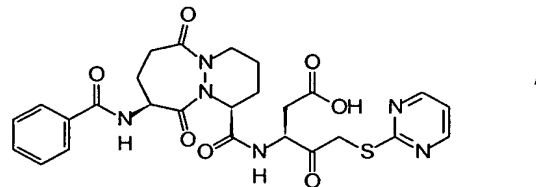
280



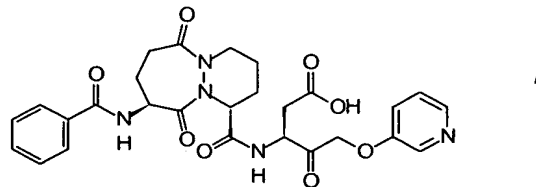
281



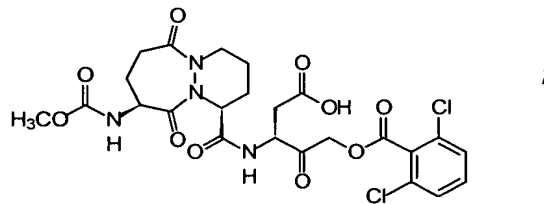
282



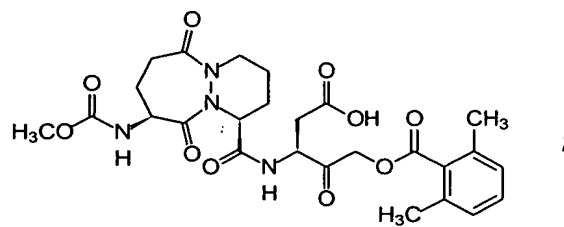
283



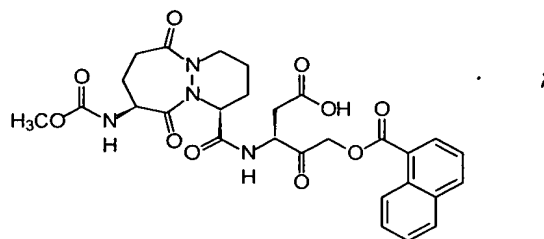
284



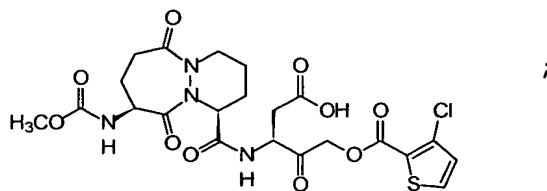
285



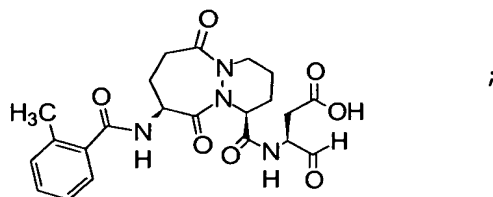
286



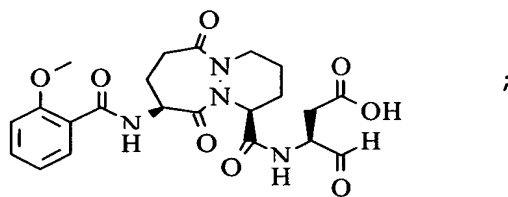
287



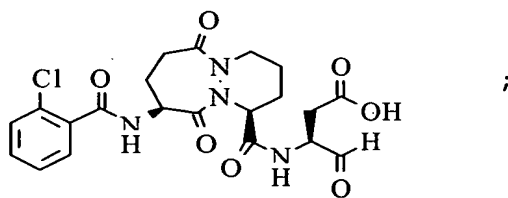
404



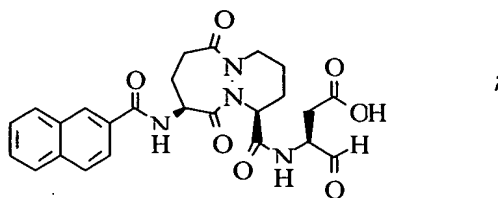
405



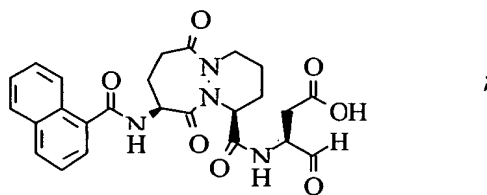
406



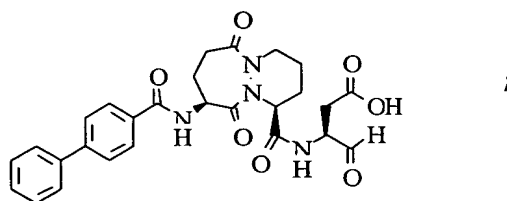
407



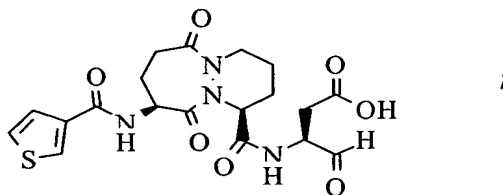
408



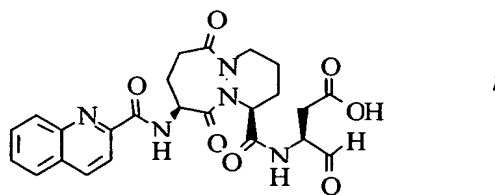
409



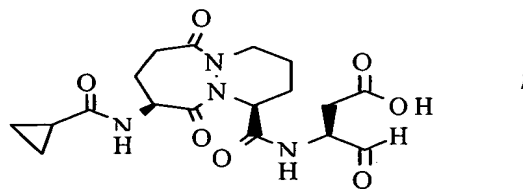
410



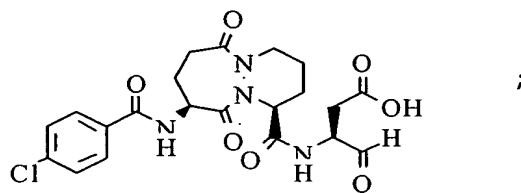
411



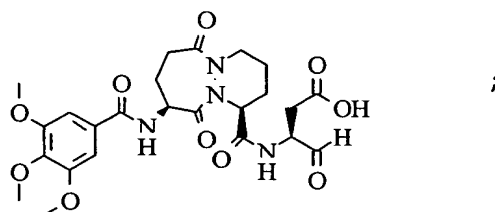
413



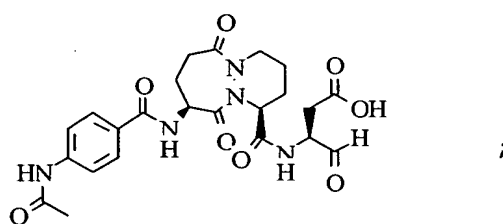
416



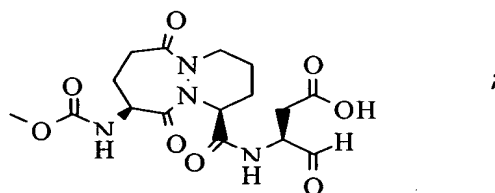
417



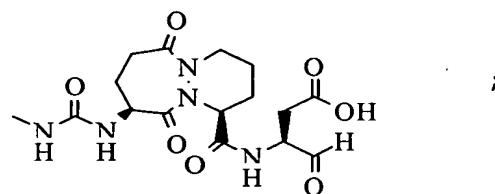
418



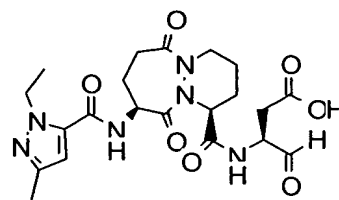
419



420

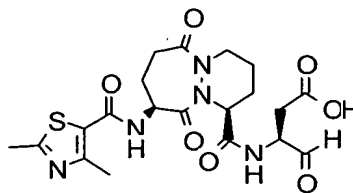


422



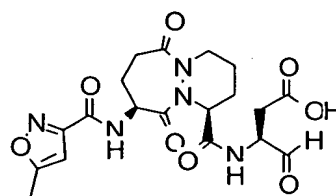
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423



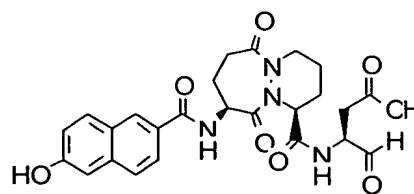
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424



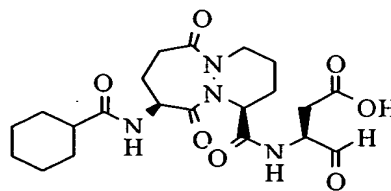
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425



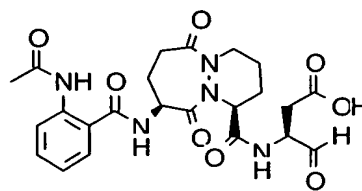
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426



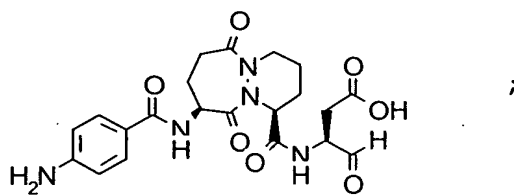
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430

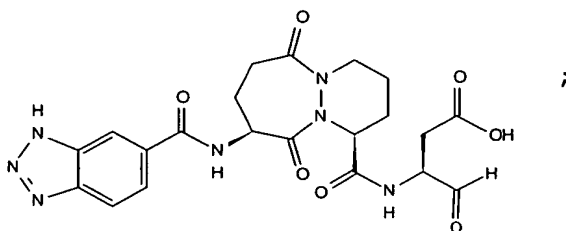


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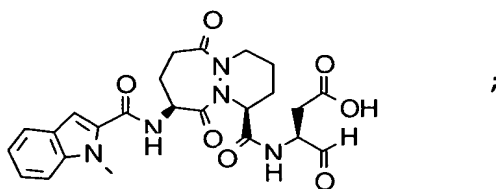
431



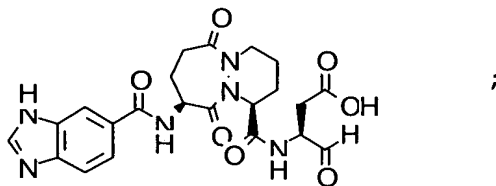
432



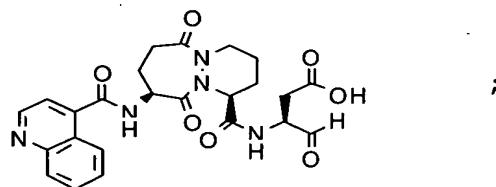
433



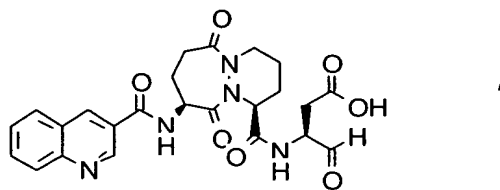
434



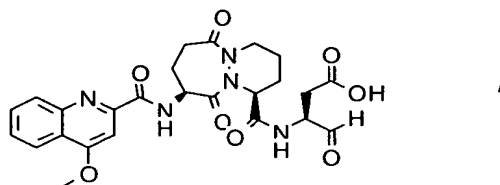
435



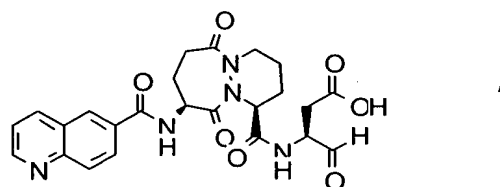
436



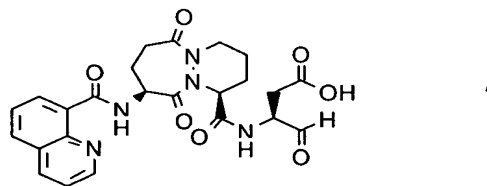
437



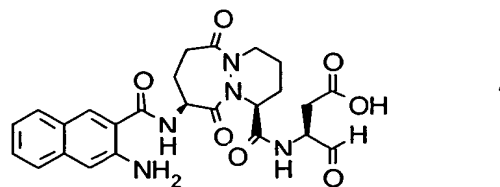
438



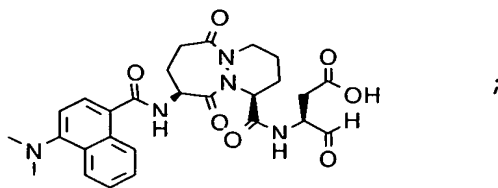
439



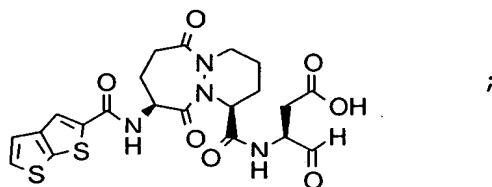
440



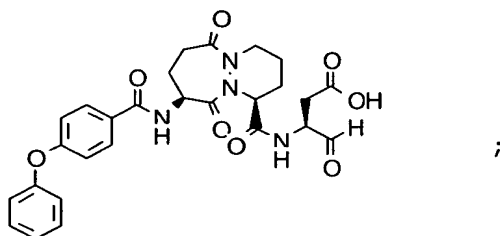
441



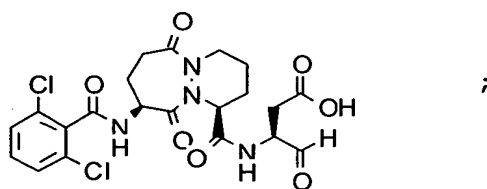
442



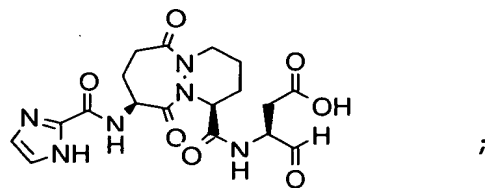
443



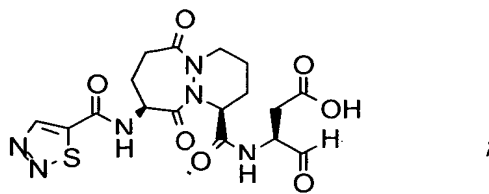
444



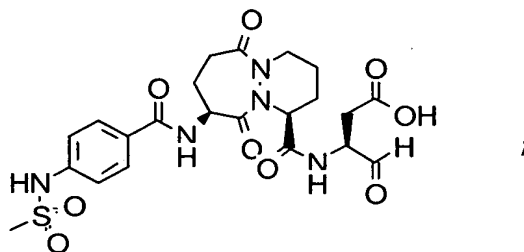
445



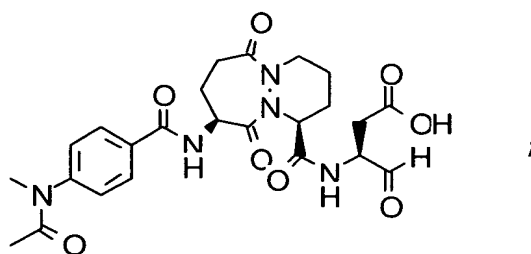
446



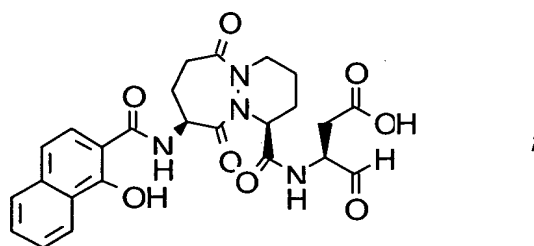
447



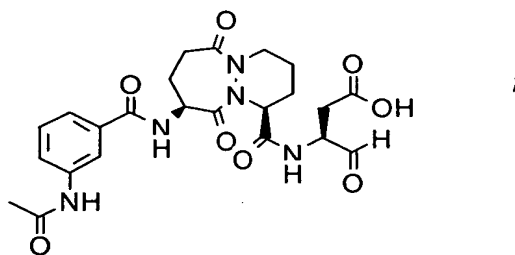
448



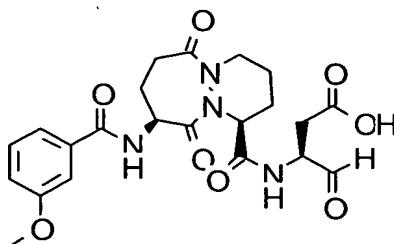
449



450

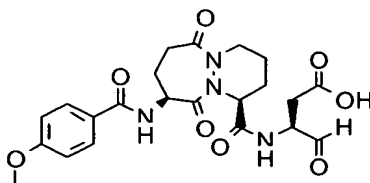


451



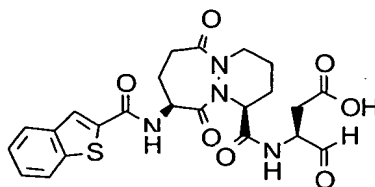
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452



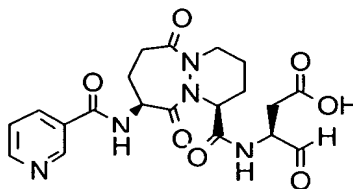
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453



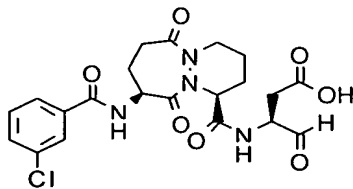
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454



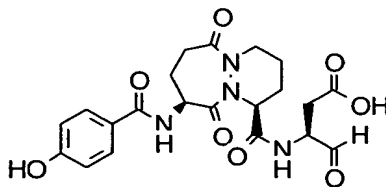
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455



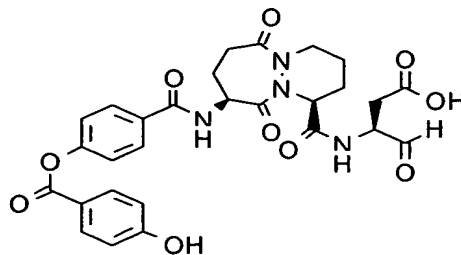
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456



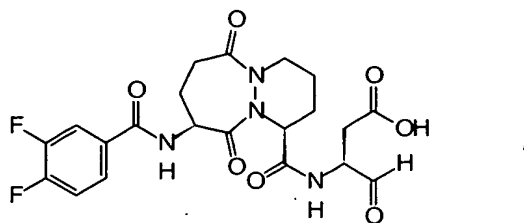
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457

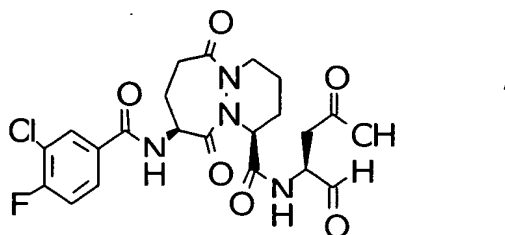


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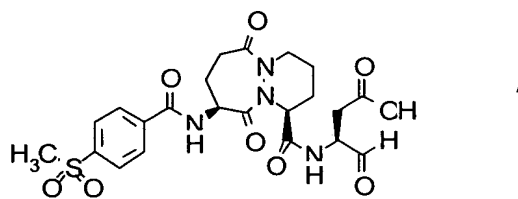
458



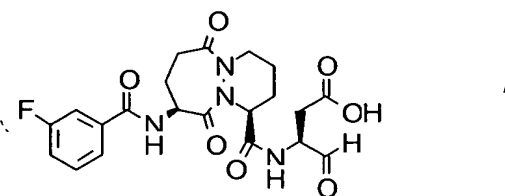
459



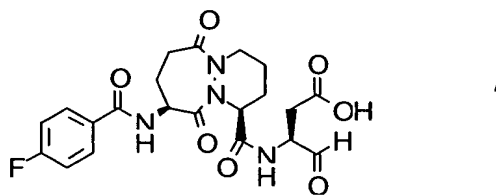
460



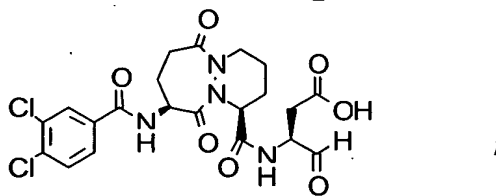
462



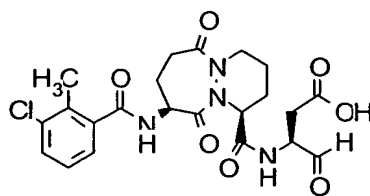
463



464

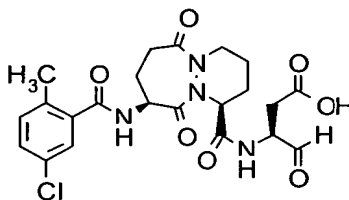


465



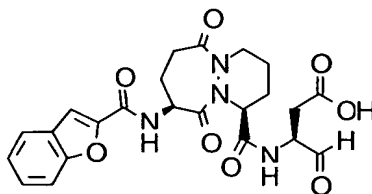
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466



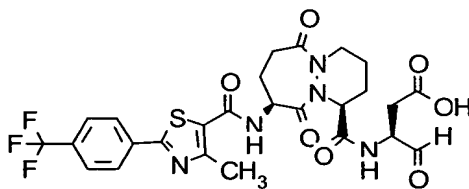
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467



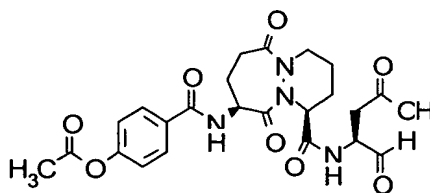
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468



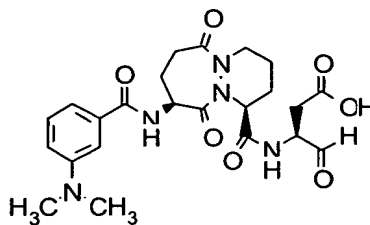
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469



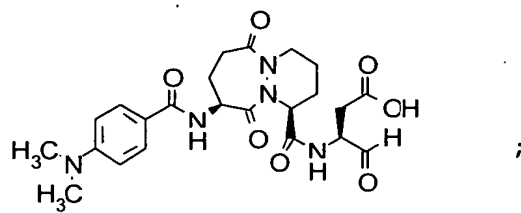
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470

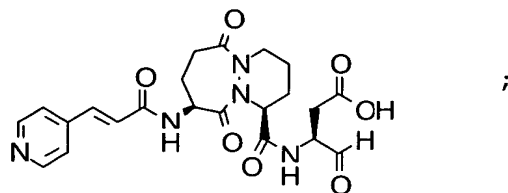


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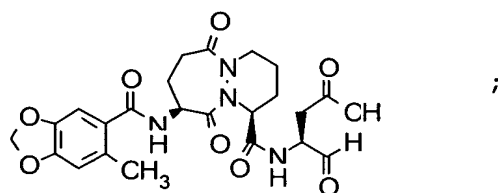
471



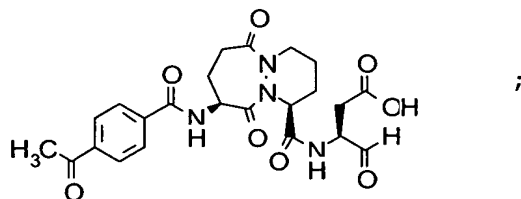
472



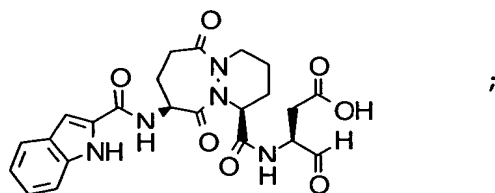
473



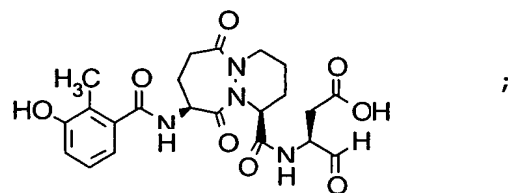
474



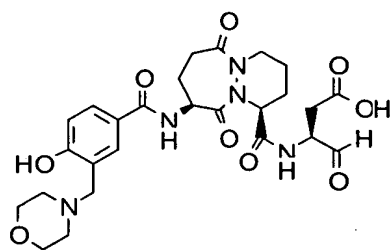
475



476

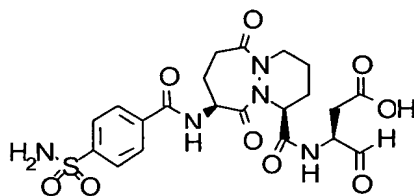


477



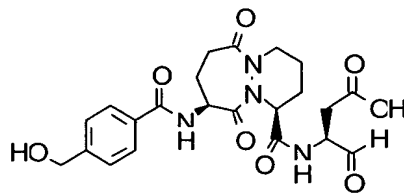
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478



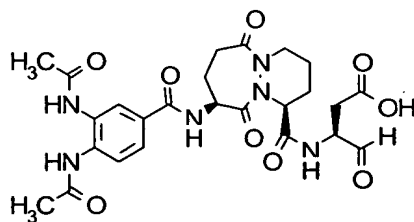
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479



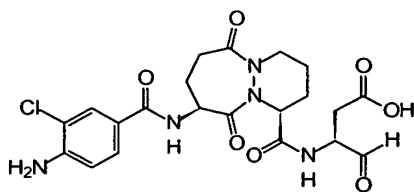
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480



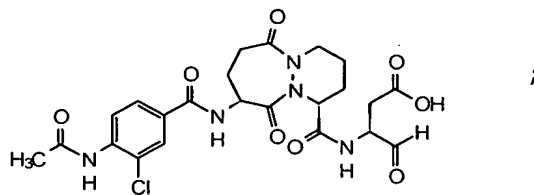
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481

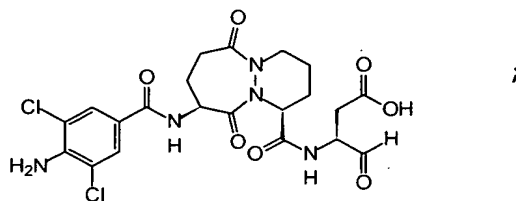


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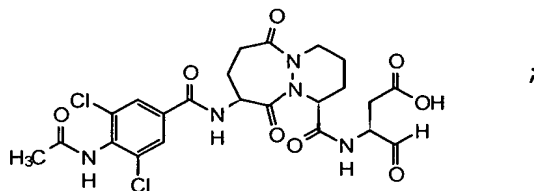
481s



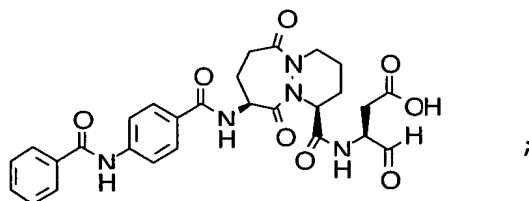
482



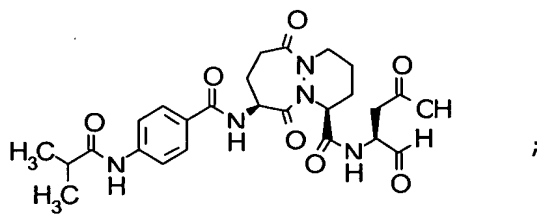
482s



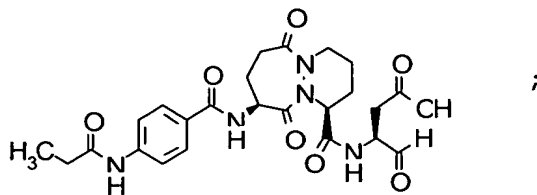
483



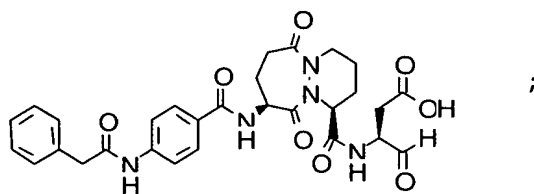
484



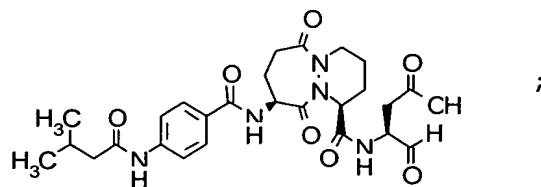
485



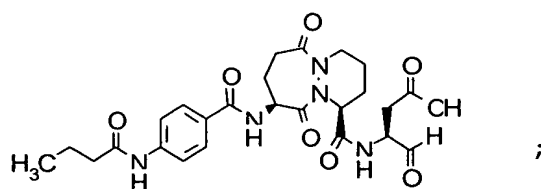
486



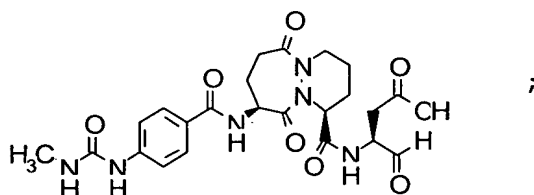
487



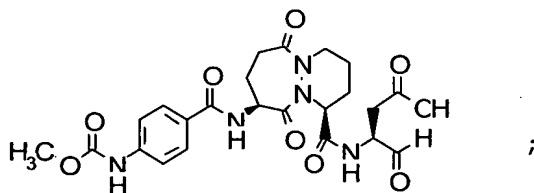
488



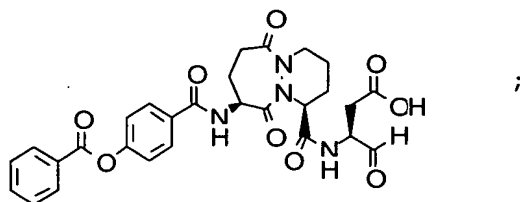
489



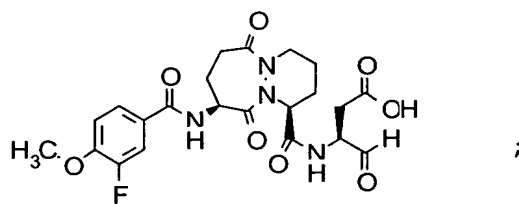
490



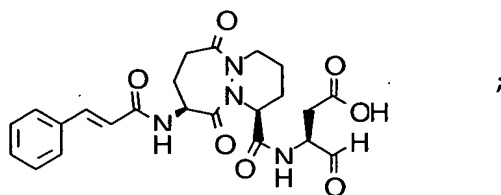
491



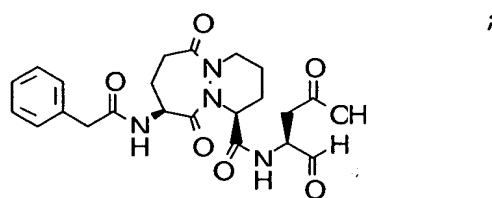
493



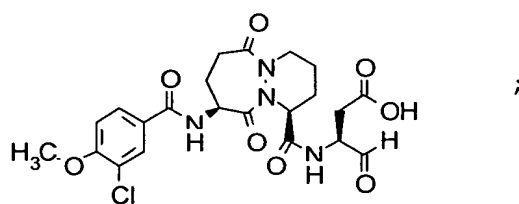
494



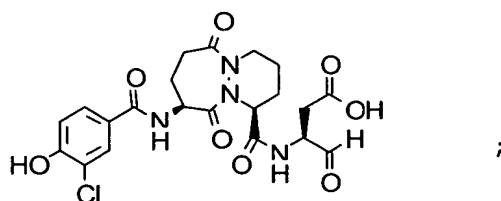
495



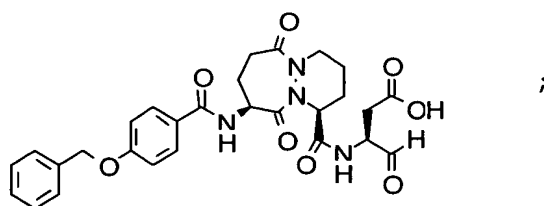
497



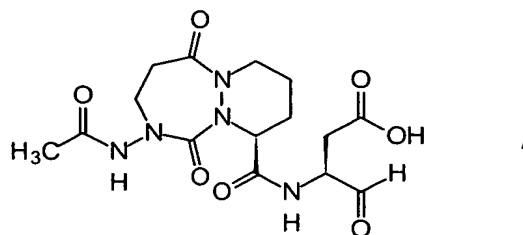
498



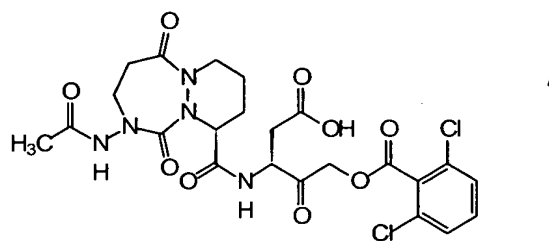
499



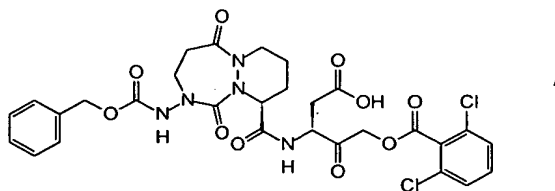
814c



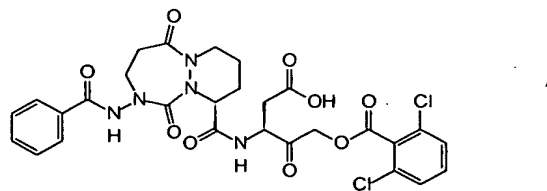
817c



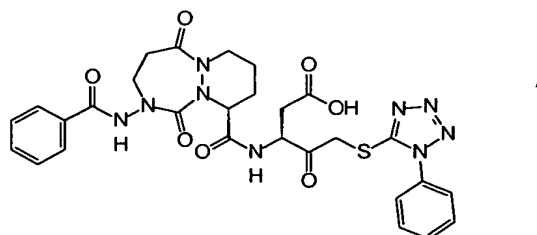
817d



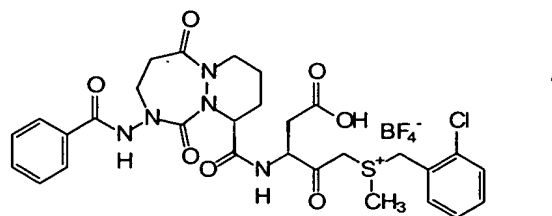
817e



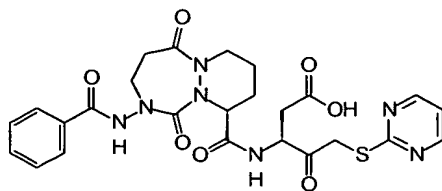
880



881

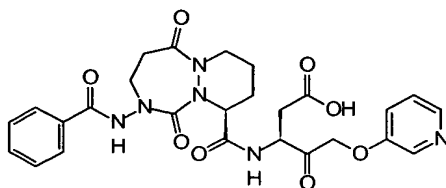


882



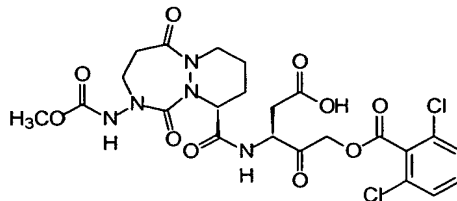
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883



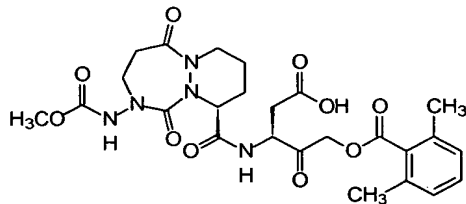
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884



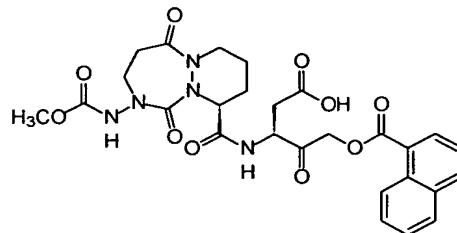
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885



;

886



;

COC(=O)N1C(=O)N2C(=O)N(C(=O)NCC(=O)OCCOC(=O)c3cc(Cl)sc3)CC2C1=O

1

CC1=CC=CC=C1C(=O)NN2C(=O)N3CCCCN3C(=O)N2C(=O)NC(=O)C(=O)O

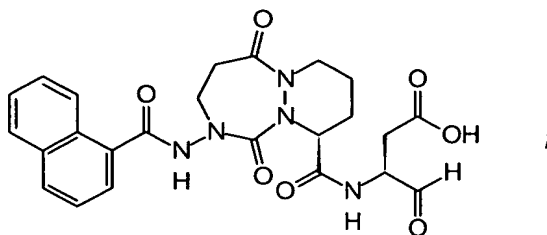
1

COC(=O)c1ccccc1NC(=O)N2C(=O)N3CCCCC3C(=O)N2C(=O)NC(=O)CC(=O)O

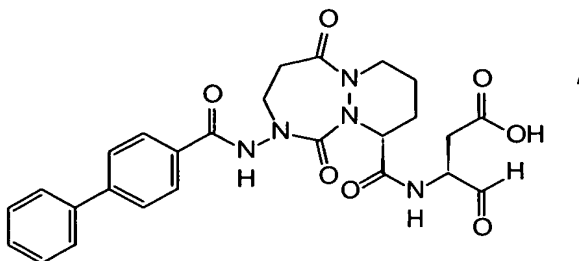
1

O=C(O)CCNC(=O)N1C(=O)N2CCCC2C(=O)N1NC(=O)c3ccccc3ClO=C(O)CCNC(=O)N1C(=O)N2CCCC2C(=O)N1C(=O)N3C(=O)c4ccc5ccccc45

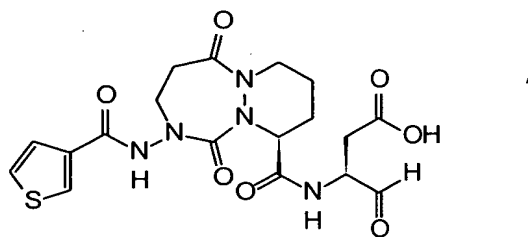
1008



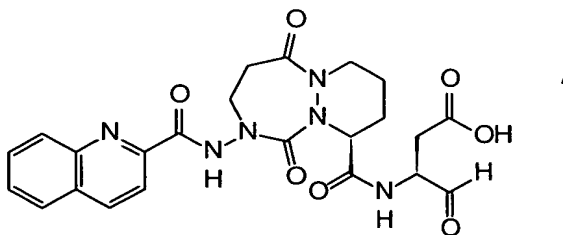
1009



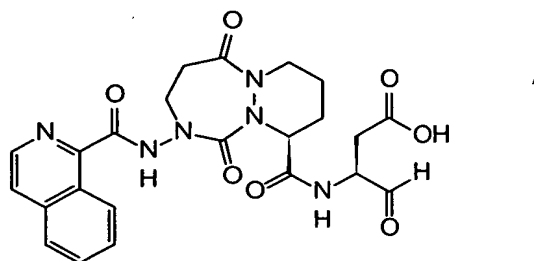
1010



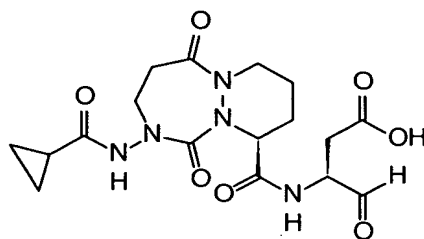
1011



1012

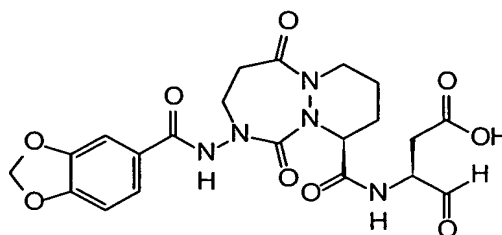


1013



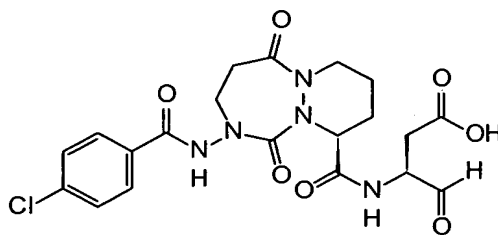
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1015



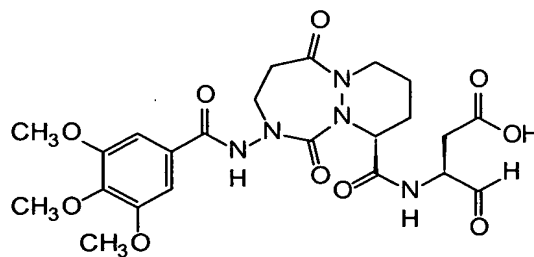
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1016



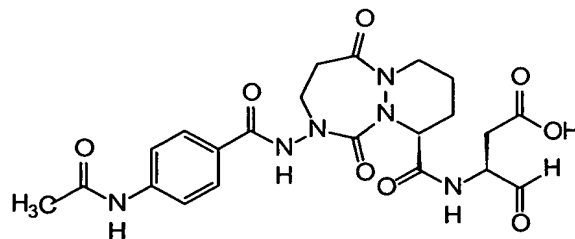
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1017



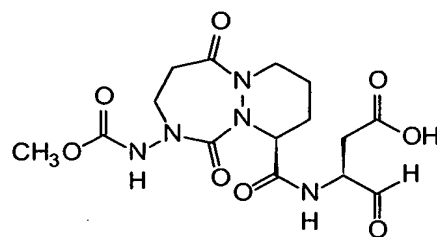
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1018



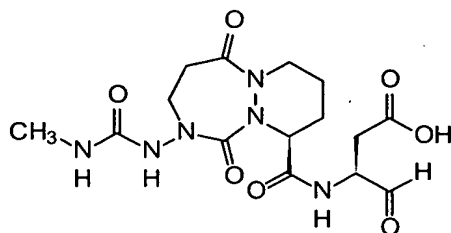
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1019



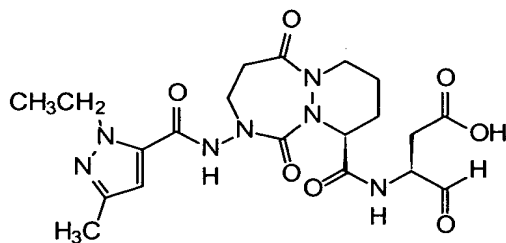
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1020



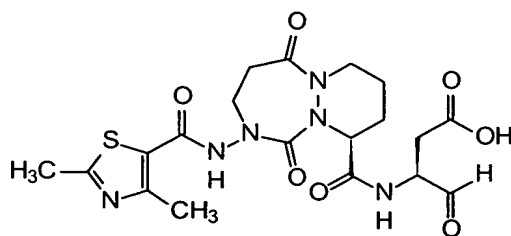
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1022



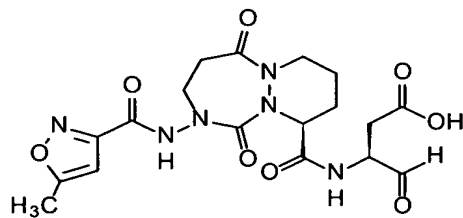
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1023



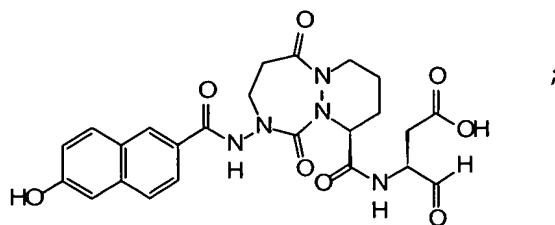
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1024

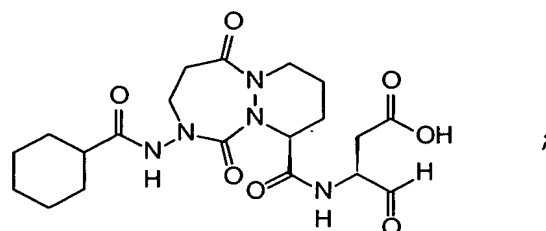


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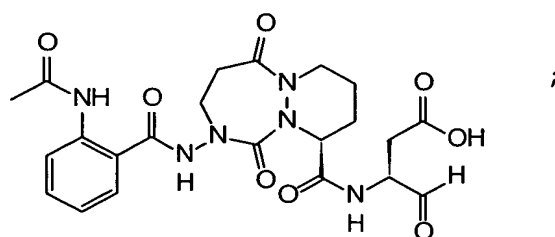
1025



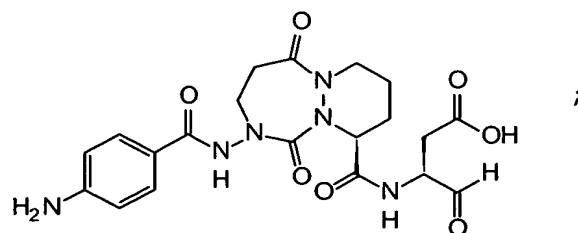
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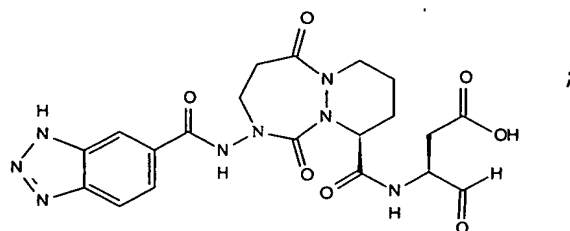
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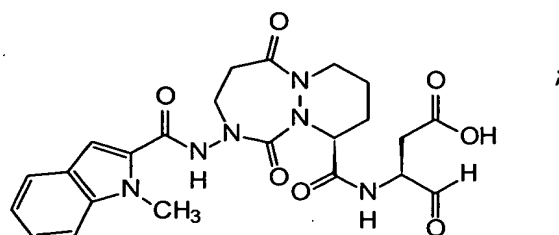
1031



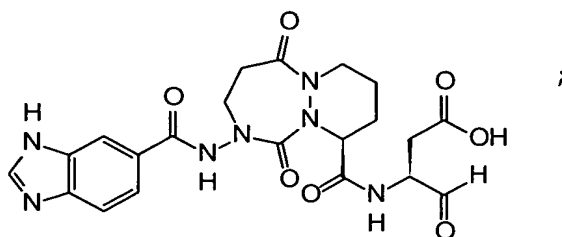
1032



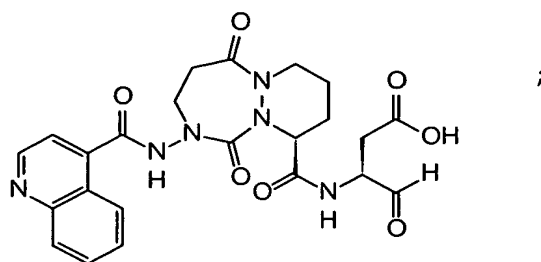
1033



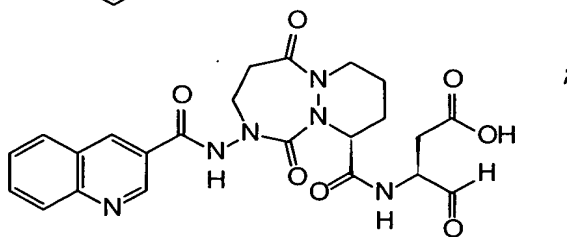
1034



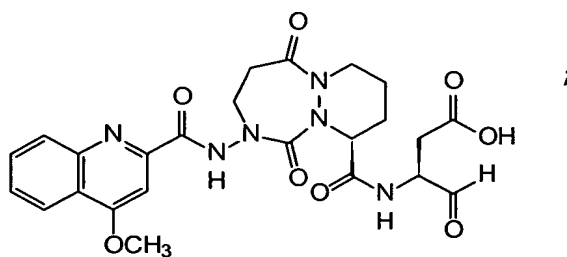
1035



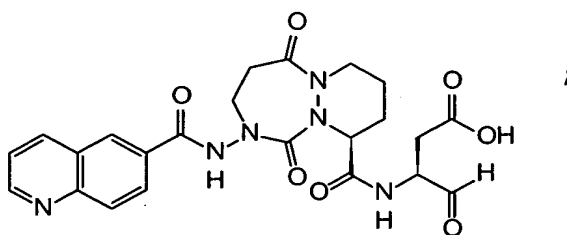
1036



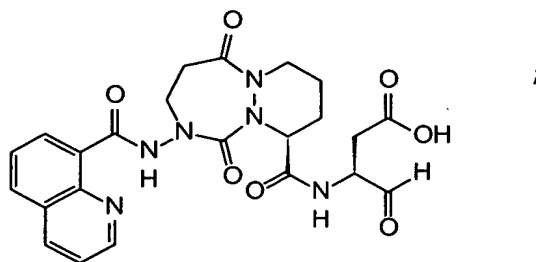
1037



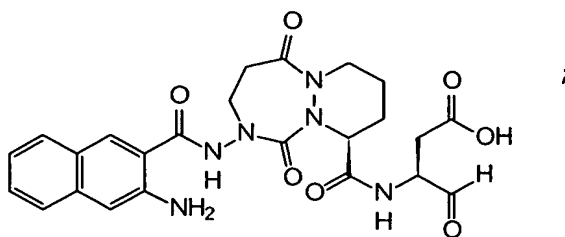
1038



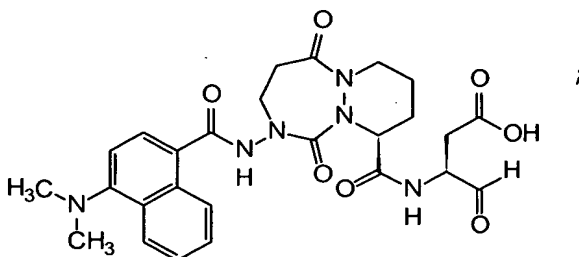
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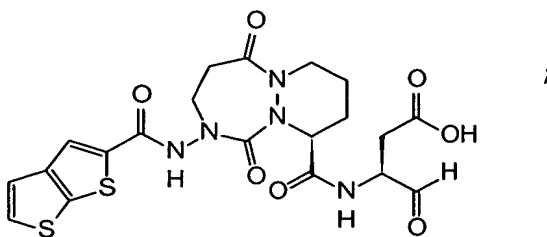
1040



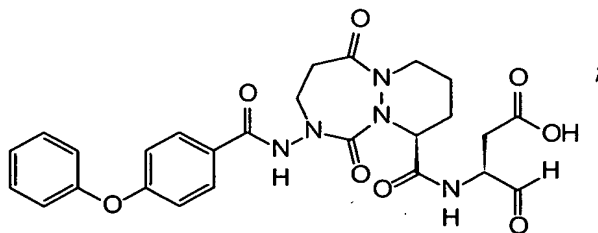
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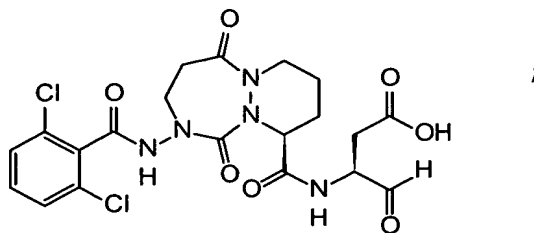
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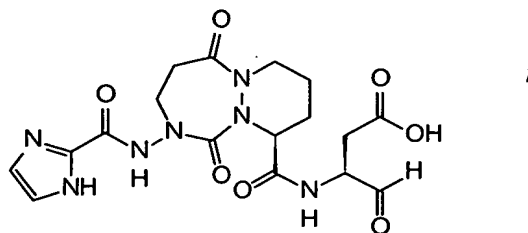
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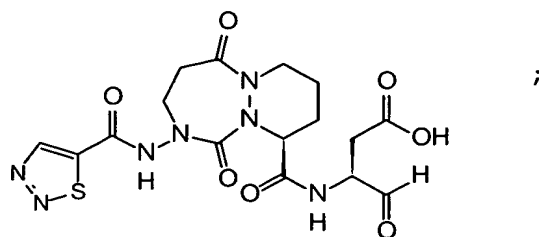
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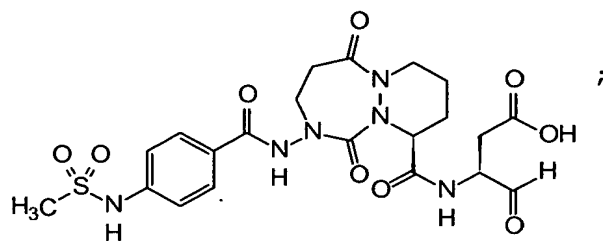
1045



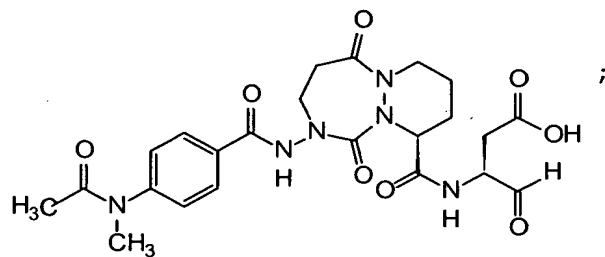
1046



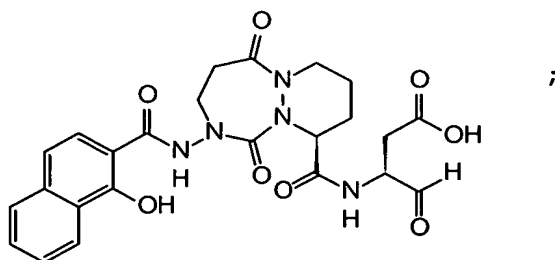
1047



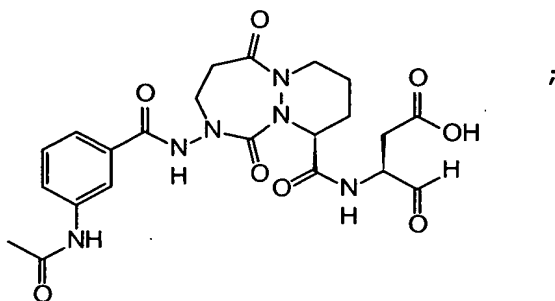
1048



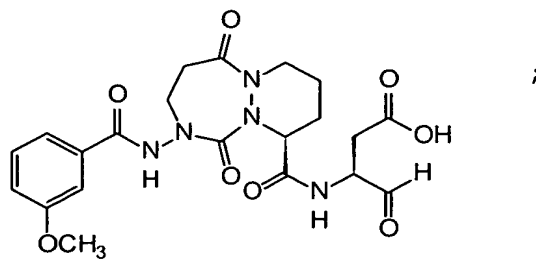
1049



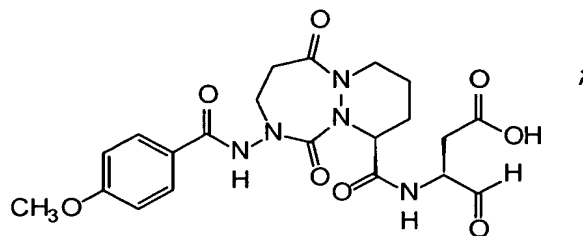
1050



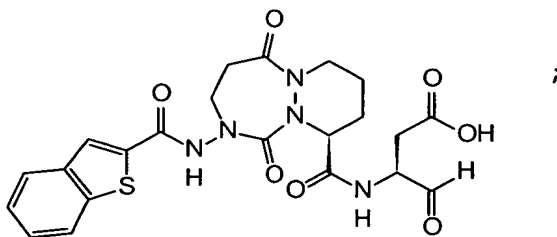
1051



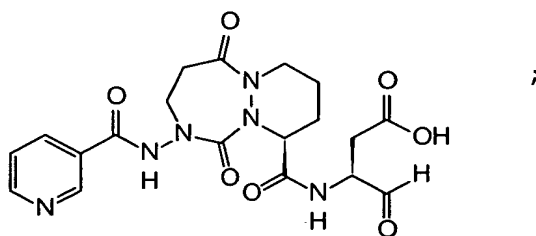
1052



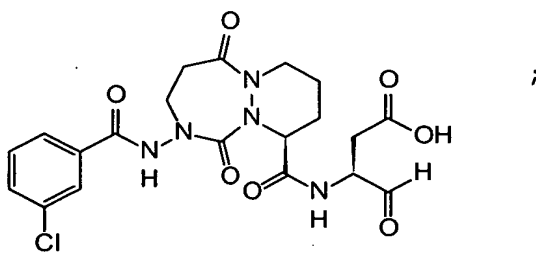
1053



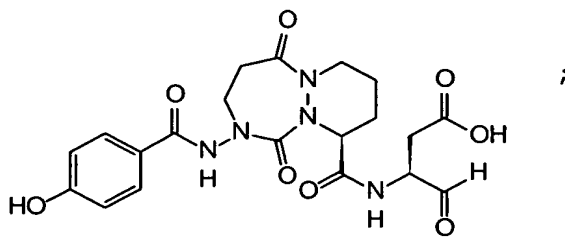
1054



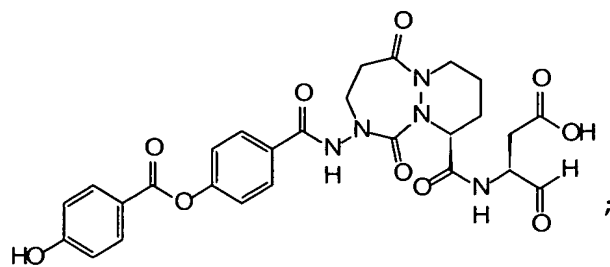
1055



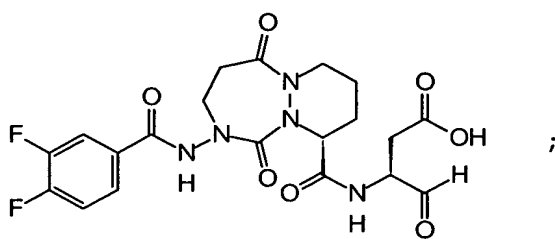
1056



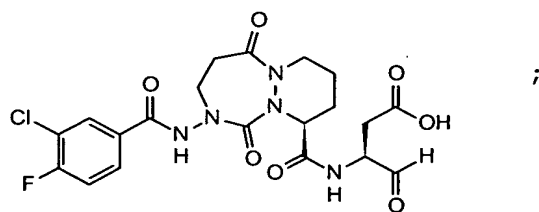
1057



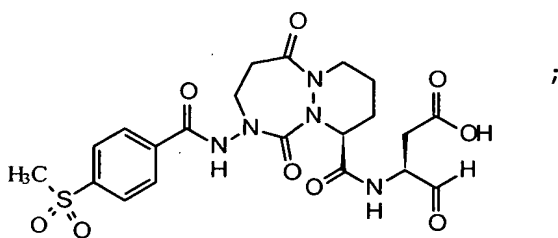
1058



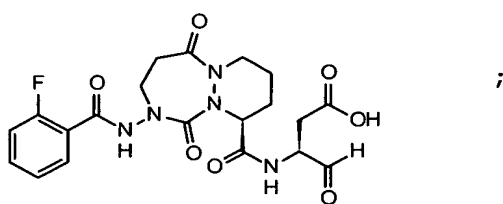
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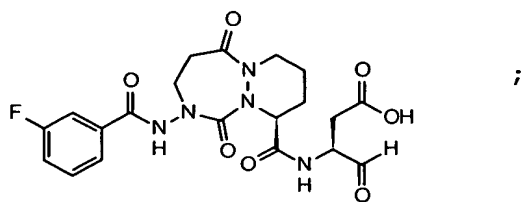
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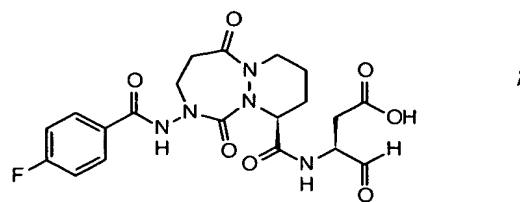
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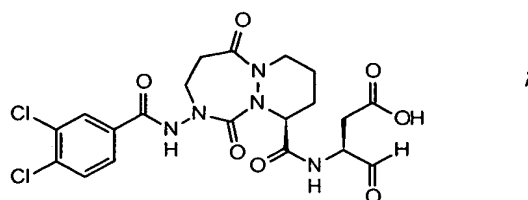
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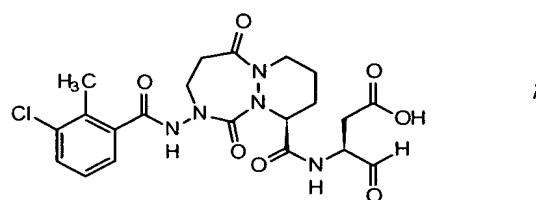
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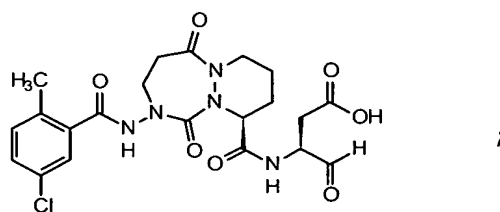
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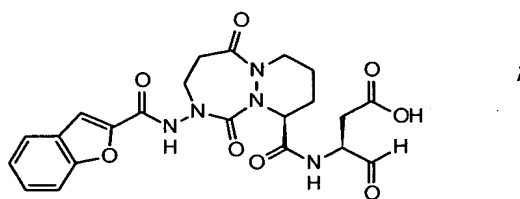
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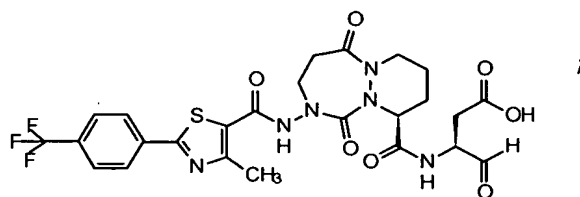
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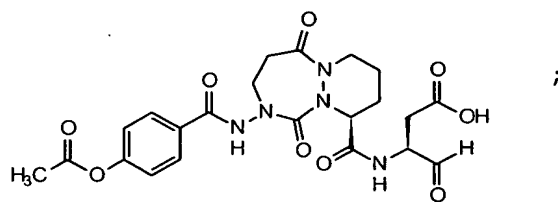
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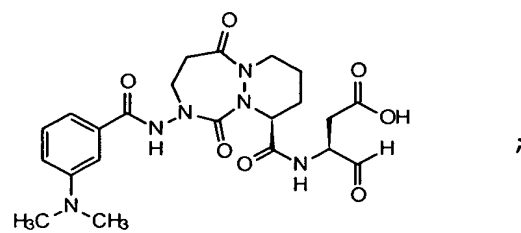
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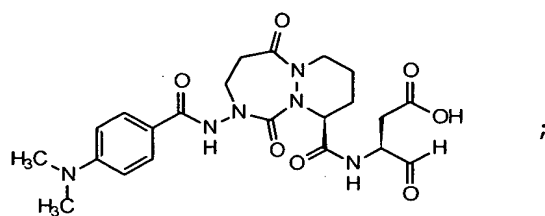
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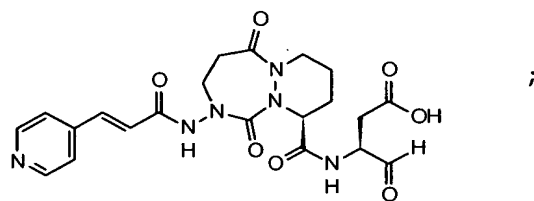
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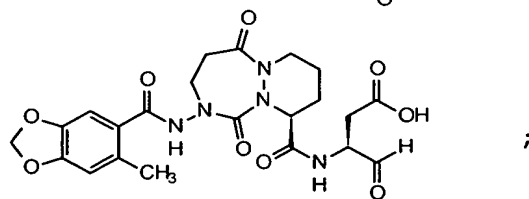
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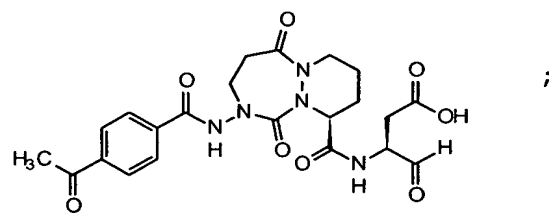
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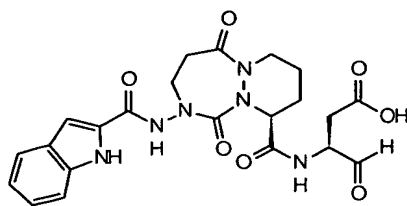
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1074

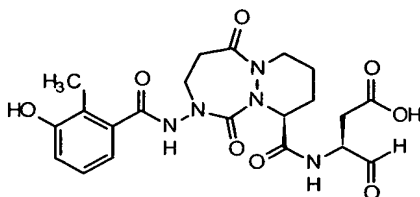


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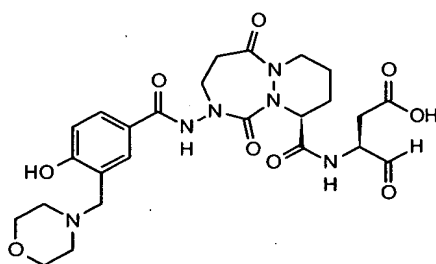
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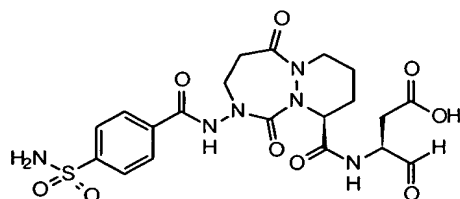
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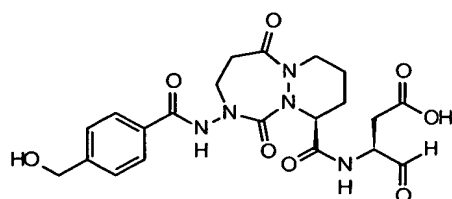
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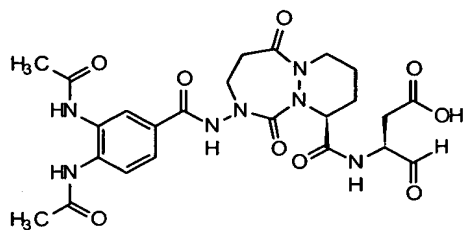
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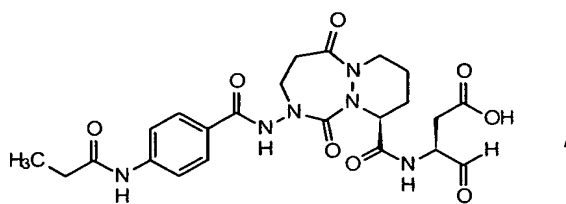
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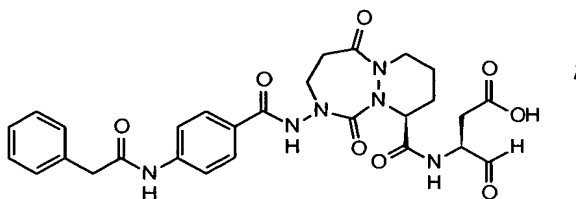


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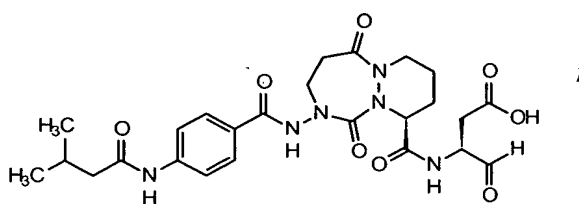
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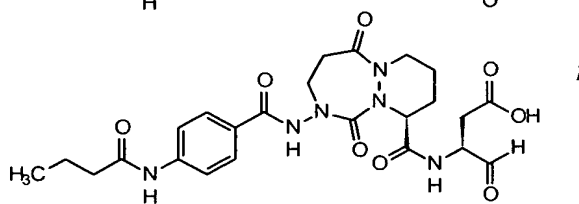
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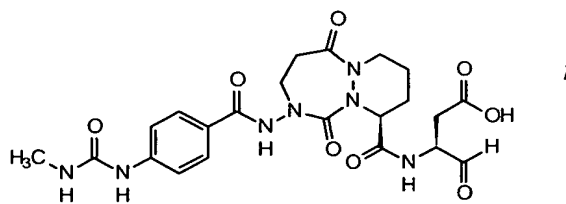
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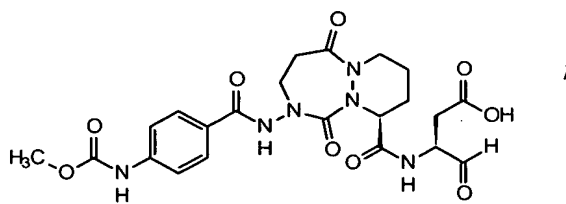
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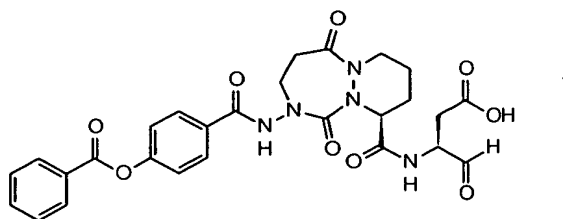
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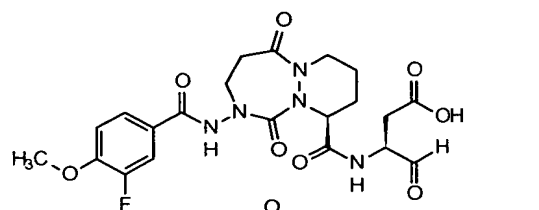
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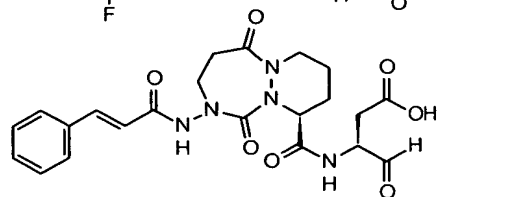
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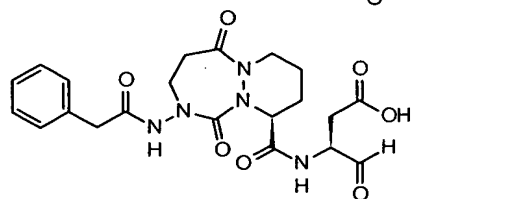
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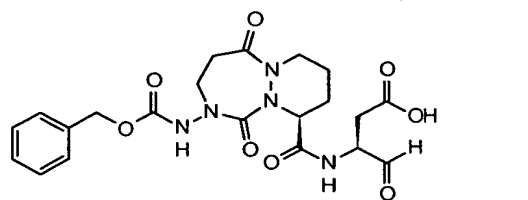
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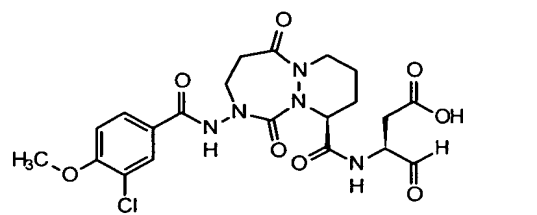
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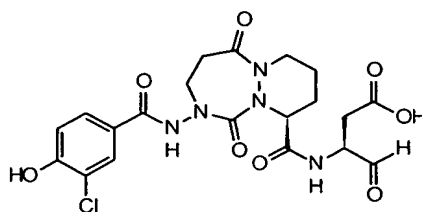
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1097

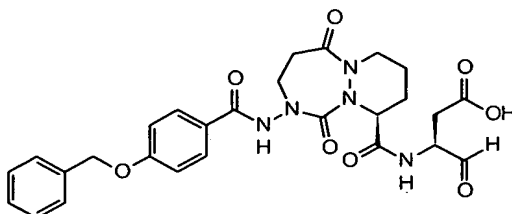


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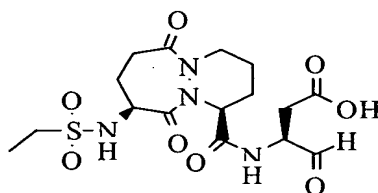


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; [and]
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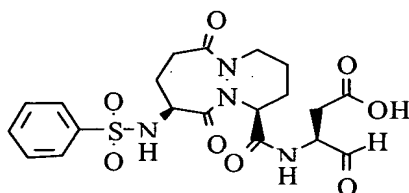
1099


$$[.]_i$$

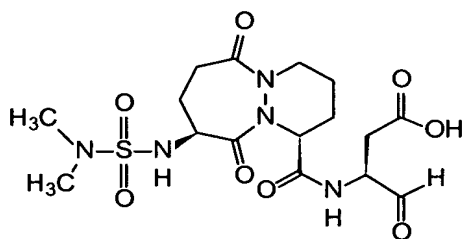
421

*i*

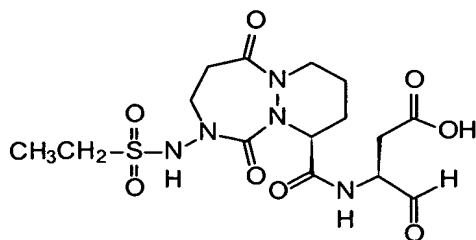
427

*i*

428

*i.*

1021

*i*

disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke in a patient comprising the step of administering to said patient a pharmaceutical composition according to [any one of claims] claim 42 [to 54].

88. The compound according to [any one of claims 80-87] claim 80, wherein R_5 is $-C(O)-R_{10}$ or $-C(O)-C(O)-R_{10}$.

118. The compound according to [any one of claims 104-117,] claims 104 or 114, wherein R_5 is $-C(O)-R_{10}$ or $-C(O)C(O)-R_{10}$.

138. A method for treating or preventing a disease selected from an IGIF mediated disease, an IFN- γ mediated disease, an inflammatory disease, an autoimmune disease, an infectious disease, a proliferative disease, a

neurodegenerative disease, a necrotic disease, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia, adult respiratory distress syndrome, infectious hepatitis, sepsis, septic shock, Shigellosis, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome comprising the step of administering to said patient a pharmaceutical composition according to [claims 136 or 137] claim 42.